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Managing the complexities of advanced cancer therapies: considerations for clinicians

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Expert Review of Hematology

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ierr20

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To cite this article: Eleftheria Kampouri, Carla S. Walti, Jordan Gauthier & Joshua A. Hill (2022) Managing hypogammaglobulinemia in patients treated with CAR-T-cell therapy: key points for clinicians, Expert Review of Hematology, 15:4, 305-320, DOI: 10.1080/17474086.2022.2063833

To link to this article: https://doi.org/10.1080/17474086.2022.2063833

EXPERT REVIEW OF HEMATOLOGY
2022, VOL. 15, NO. 4, 305–320
https://doi.org/10.1080/17474086.2022.2063833

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REVIEW

Managing hypogammaglobulinemia in patients treated with CAR-T-cell therapy: key points for clinicians

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ABSTRACT

Introduction: The unprecedented success of chimeric antigen receptor (CAR)-T-cell therapy in the management of B-cell malignancies comes with a price of specific side effects. Healthy B-cell depletion is an anticipated 'on-target' 'off-tumor' side effect and can contribute to severe and prolonged hypogammaglobulinemia. Evidence-based guidelines for the use of immunoglobulin replacement therapy (IGRT) for infection prevention are lacking in this population.

Areas Covered: This article reviews the mechanisms and epidemiology of hypogammaglobulinemia and antibody deficiency, association with infections, and strategies to address these issues in CD19- and BCMA-CAR-T-cell recipients.

Expert Opinion: CD19 and BCMA CAR-T-cell therapy result in unique immune deficits due to depletion of specific B-lineage cells and may require different infection prevention strategies. Hypogammaglobulinemia before and after CAR-T-cell therapy is frequent, but data on the efficacy and cost-effectiveness of IGRT are lacking. Monthly IGRT should be prioritized for patients with severe or recurrent bacterial infections. IGRT may be more broadly necessary to prevent infections in BCMA-CAR-T-cell recipients and children with severe hypogammaglobulinemia irrespective of infection history. Vaccinations are indicated to augment humoral immunity and can be immunogenic despite cytopenias; re-vaccination(s) may be required. Controlled trials are needed to better understand the role of IGRT and vaccines in this population.

ARTICLE HISTORY
Received 22 December 2021
Accepted 5 April 2022

KEYWORDS
CAR-T-cell therapy; CD19; BCMA; infection; IgG replacement therapy; IVIG; hypogammaglobulinemia; B-cell aplasia; vaccination; COVID-19

1. Introduction

Chimeric antigen receptor (CAR)-modified-T-cell immunotherapy is rapidly transforming the landscape of cancer care. This treatment induces durable complete remissions in a majority of heavily pretreated patients with relapsed/refractory (R/R) hematologic malignancies including B-cell acute lymphoblastic leukemia (ALL), B-cell non-Hodgkin lymphomas and more recently multiple myeloma (MM) [1-6]. Several CD19-targeted CAR-T-cell products have now been approved by the US Food and Drug Administration (FDA) and include: tisagenlecleucel (Kymriah; Novartis) for R/R B-cell ALL and large B-cell lymphomas [1,2], axicabtagene ciloleucel (Yescarta: Kite/Gilead) and lisocabtagene maraleucel (Breyanzi; Juno/BMS) for R/R large B-cell lymphoma and follicular lymphoma [3,4], and brexucabtagene autoleucel (Tecartus; Kite/Gilead) for R/R mantle cell lymphomas and B-ALL [5]. Most recently, idecabtagene vicleucel (Abecma; Celgene/BMS), targeting B cell maturation antigen (BCMA), was the first CAR-T-cell product to be approved for R/R MM [6]. CAR-T-cell therapy is the first therapeutic approach utilizing a genetic engineering technology to ever gain commercial approval. Beyond the FDA approved CAR-T-cell products, hundreds of ongoing clinical trials currently investigate additional CAR-T-cell products, tumor antigen targets and the expansion of use of CAR-T-cells in various hematologic malignancies [7], solid tumors [8], and in non-oncological indications such as infectious and auto-immune diseases [9].

CARs are synthetic receptors designed to redirect the specificity of T lymphocytes to a target molecule on the surface of malignant cells and are composed of an extracellular, antibody-derived, targeting domain and an intracellular signaling domain derived from T-cell signaling proteins (CD3ζ), fused to costimulatory domains (e.g. CD28, 4–1BB) in 2nd and 3rd generation CARs. The costimulatory domains are crucial for the in vivo expansion of CAR-T-cells allowing them to persist for months to years and produce durable effects, granting them their function as 'living drugs.' Autologous T-cells are genetically modified to express the CAR on their surface using mostly viral vectors as gene delivery systems (transduction). CAR-T-cells are then expanded and infused into a patient previously treated with lymphodepleting conditioning chemotherapy, where they identify, bind to, and kill cancer cells in a process leading to CAR-T-cell proliferation, systemic inflammation (cytokine release syndrome), release of tumor antigens and activation of endogenous immune effector cells [10–12].

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Article highlights

- Prolonged B-cell aplasia and hypogammaglobulinemia are commonly reported following CAR-T-cell therapy, but the clinical impact of hypogammaglobulinemia on infection risk is not well elucidated.
- CD19 and BCMA CAR-T-cell therapies induce distinct humoral immune deficits due to the expression of their targets in distinct stages of differentiation of normal B-lineage cells and could require different clinical approaches for infection prevention that should stem from prospective studies and clinical trials.
- There is growing evidence of at least partially maintained pathogen-specific IgG levels following CD19 CAR-T-cell therapy. In contrast, there is evidence for poor maintenance of pathogen-specific IgG levels prior to and after BCMA-targeted CAR-T-cell therapy, which may be attributable to the depletion of long-lived plasma cells. Memory B-cell pools may need to be re-established independent of CAR-T-cell type.
- Infection risk is high in CAR-T-cell recipients due to a plethora of host- and treatment-related factors. Infection density is higher within the first month following CAR-T-cell infusion and decreases subsequently. Bacterial infections are more frequent in the early period while viral infections predominate later.
- There is limited evidence supporting prophylactic IgG replacement in CAR-T-cell recipients. In light of the adverse events, costs and limited access, routine IgG replacement should be carefully evaluated and prioritized in patients with severe or recurrent bacterial infections. More intensive IgG replacement strategies should be considered in pediatric patients and BCMA-targeted CAR-T-cell recipients.
- IgG levels may not be an adequate biomarker of humoral immunodeficiency, and multiple aspects of the clinical condition of a patient should be used to guide the decision of whether and when to initiate IgG replacement. More sophisticated tools for risk stratification and clinical decision making are needed.
- Hypogammaglobulinemia does not preclude adequate vaccine responses, but vaccine immunogenicity generally is low in CAR-T-cell recipients.
- Current vaccine recommendations are extrapolated from other immunocompromised populations and future studies are needed to define the need and timing for revaccination and to identify factors associated with vaccine immunogenicity in CAR-T-cell therapy recipients.
- As CAR-T-cell therapies continue to expand, infection prevention and management strategies are becoming increasingly crucial to optimize outcomes in a growing population of CAR-T-cell recipients.

CAR-T-cell recipients are often highly immunosuppressed. This can be due to factors related to the underlying malignancy and previous treatments such as hematopoietic cell transplantation (HCT) and to the CAR-T-cell therapy itself; this includes lymphodepletion chemotherapy and bridging chemo-immunotherapies, and post CAR-T-cell infusion toxicities [13–15]. Neutropenia due to the conditioning chemotherapy is almost universally present after CAR-T-cell infusion; severe neutropenia (<500 cell per mm^3) occurs in over 70% of the patients and can have a prolonged course in up to two thirds of patients [16–19]. The severity and duration of neutropenia is a key determinant of infection risk early after CAR-T-cell infusion with most infections being bacterial and occurring during the neutropenic phase, usually within the first 10 days after infusion [20,21], while prolonged neutropenia is a major risk factor for invasive fungal infections [22]. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) are frequent acute toxicities and reflect the robust activation of CAR-T-cells and their interaction with bystander endogenous immune effector and cancer cells leading to massive cytokine release and endothelial damage [23]. The management of these acute toxicities relies on corticosteroids for ICANS and corticosteroids/anti-interleukin-6 agents for CRS, which contribute to additional immune suppression [24–26]. The profound immune dysregulation related to these acute toxicities, and the additional immunosuppression used for their management, increase the infectious risk. Indeed, CRS is identified as a major risk factor for infection in some clinical studies [20,21]. Moreover, invasive procedures to manage critically ill patients add to the already high infection risk during the early period after CAR-T-cell infusion.

1.1. 'On-target' 'off-tumor' effects of CAR-T-cell therapies: the pathophysiology behind hypogammaglobulinemia

The specific engagement of CAR-T-cells with their targets on non-malignant B-lineage cells, known as 'on target' 'off tumor' effects, can lead to persistent B-cell aplasia, which may contribute to hypogammaglobulinemia [13,14,27,28]. Other mechanisms like cytokine and/or chemokine-induced effects are potentially also involved, as additional hematopoietic cell lines not carrying CAR-T-cell targets may be affected, resulting in prolonged cytopenias [16,19,29]. The antigen targets of CAR-T-cells, which are expressed in distinct stages of normal B-lineage cells, define the nature of these 'on-target' but undesirable effects and shape the distinct immune deficits related to different CAR-T-cell targets [13]. The main B-cell populations in the peripheral blood are $CD19^+$, $BCMA^-$, non-antibody-producing naïve and memory B-cells that develop into antibody-producing plasma blasts and plasma cells upon exposure to a matching antigen [30]. Thus, their depletion potentially contributes to insufficient antibody responses to neo-antigens or antigen re-exposures. Profound B-cell depletion in the peripheral blood was reported in more than 85% of CD19 CAR-T-cell recipients within a month following CAR-T-cell therapy and in 42–60% of those with ongoing oncologic remission at 1 year [1,20,29,31]. Peripheral blood B-cell depletion and decreased memory B-cell levels have also been reported in BCMA CAR-T-cell recipients, highlighting the potential need to re-establish pathogen-specific memory B-cells after either CD19 or BCMA-directed CAR-T-cell therapy [32].

Relatively short-lived $CD19^+$, $BCMA^+$ plasma blasts and plasma cells are the source of transiently increased antibody levels following infection, while long-lived plasma cells expressing BCMA but typically lacking CD19 are thought to be responsible for maintaining relatively stable concentrations of antigen-specific antibodies against previously encountered pathogens [33]. One study involving bone marrow biopsies demonstrated elimination of $CD19^+$, $BCMA^+$ plasma cells, but persistence of $CD19^-$, $BCMA^+$ plasma cells following CD19 CAR-T-cell therapy leading to a discrepancy between total and pathogen-specific antibody levels in this population [34]. In contrast, all plasma cell populations seem to be depleted following BCMA CAR-T-cell therapy potentially leading to more severe antibody deficiencies [28,35] (Figure 1).

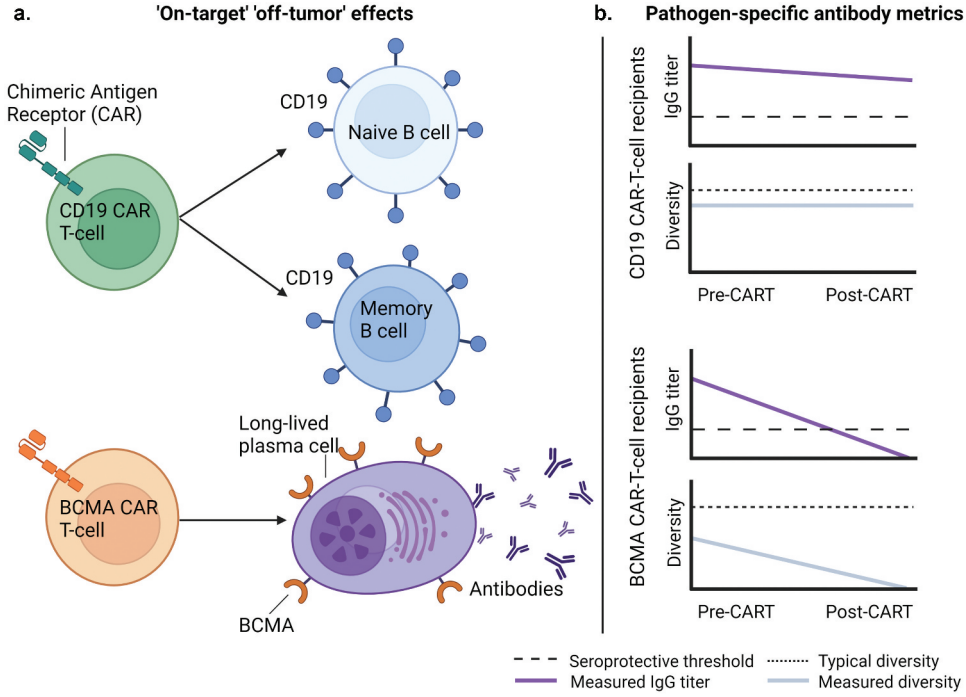

Figure 1. On-target, off-tumor effects of CD19 and BCMA-targeted CAR T-cells.

(a) CD19 is expressed on all stages from pre-B-cells to memory B cells but not on all long-lived antibody-producing plasma cells [34]. BCMA is absent in naïve and most memory B-cells but is expressed on late-stage memory B-cells (committed to plasma cell differentiation), short-lived proliferating plasma blasts, and long-lived plasma cells and is important for long-lived plasma cell survival [36]. (b) The effect on antibody levels and diversity according to targeted antigen. Figure has been adapted from Hill JA et al., Blood 2020 [15] and Hill JA et al., Blood Advances 2019 [42]. Figure created with BioRender.com.

1.2. Humoral immune deficits and opportunities for infection prevention

The impact of these humoral immune deficits on infection risk, particularly in the long-term follow-up setting, remains largely unknown. Current management guidelines are extrapolated from patients with primary immune deficiencies and other onco-hematological conditions such as patients with lymphoma treated with anti-CD20 agents or autologous HCT. Indeed, hypogammaglobulinemia or specific antibody deficiency with normal total IgG levels is common in patients with B-cell lymphoid malignancies and multiple myeloma due to the clonally proliferating B-cells and the treatments aiming to eradicate them even before CAR-T-cell therapy [37]. The added 'on-target' 'off-tumor' effects of the 'living' drugs exacerbates these pre-existing deficits and suggest a potential prophylactic role for immunoglobulin replacement therapy (IGRT) which has become a key component of follow-up care after CAR-T-cells. Moreover, the anticipated B-cell aplasia and hypogammaglobulinemia can lead to increased susceptibility to vaccine-preventable encapsulated bacteria, such as *Haemophilus influenzae* type B, *Neisseria meningitidis*, and *Streptococcus pneumoniae*, underlining the key role of vaccination in addressing pathogen-specific antibody deficits in this population. Finally, long-term antibiotic chemoprophylaxis against encapsulated bacteria with the use of trimethoprim/sulfamethoxazole or penicillin as indicated in patients with chronic graft-versus-host disease (GVHD) could be another strategy but has not been studied to date.

We review here the epidemiology of hypogammaglobulinemia, pathogen-specific antibody deficiency, and infections following CD19 and BCMA CAR-T-cell therapy. We provide suggested strategies to mitigate infection risk related to hypogammaglobulinemia, which can be broadly divided into three main pillars: IGRT, vaccination, and antibiotic chemoprophylaxis (Figure 2).

2. Hypogammaglobulinemia after CAR-T-cell therapy

2.1. IgG

Prior to CD19 and BCMA CAR-T-cell therapy, hypogammaglobulinemia already affects 16–40% of patients [20,29,31,38–41]. However, total IgG levels may decrease further following CAR-T-cell infusion, and hypogammaglobulinemia can persist for months or even years [20,29,31,38]. In a study of 85 adults with large B-cell lymphoma treated with axicabtagene ciloleucel, a CD19 CAR-T-cell product, 28% had severe hypogammaglobulinemia (IgG<400 mg/dL) before lymphodepleting chemotherapy; levels decreased further following CAR-T-cell therapy with a nadir at 6 months, and hypogammaglobulinemia was still present at 1 year in 47% of patients without IGRT [31]. In a similar investigation including 41 patients, 10% had severe hypogammaglobulinemia (IgG<400 mg/dL) before lymphodepleting chemotherapy. Total IgG levels decreased over the first 9 months following CAR-T-cell therapy, a total of 62.2% of all patients were affected by severe hypogammaglobulinemia, and 36.6% received IGRT [29]. However, reported

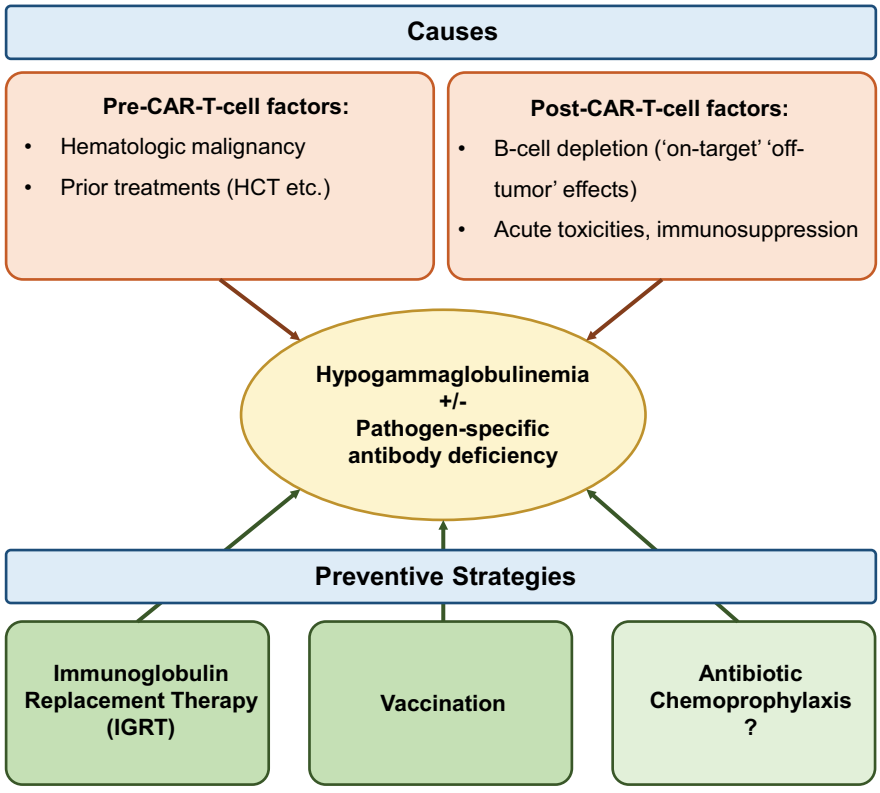

Figure 2. Strategies to mitigate infection risk due to hypogammaglobulinemia include immunoglobulin replacement therapy, vaccination, and antibiotic chemoprophylaxis.

rates of hypogammaglobulinemia vary widely between studies with different CAR-T-cell products and patient populations; hypogammaglobulinemia affected only 14% of patients treated in a phase 1/2 study with lisocabtagene maraleucel for R/R large B-cell lymphoma [4], and only 1% of the patients experienced grade 3 hypogammaglobulinemia in a phase 2 clinical trial with brexucabtagene autoleucel for mantel cell lymphoma [5]. Moreover, not all studies found large declines in total IgG levels after CD19 CAR-T-cell therapy; in a study in 39 adults with B-cell malignancies who achieved durable remission with CD19 CAR-T-cell therapy, mean total serum IgG decline was 100 mg/dL from before lymphodepleting chemotherapy to a time point within the first 100 days after CAR-T-cell therapy (mean change, −17.7%; 95% CI, −26.8 to −8.2) [42].

Among pediatric and young adult patients with B-ALL, prolonged B-cell aplasia is reported in two-thirds of patients with ongoing response at 12 and 24 months [43] and can persist for even longer (B-cell aplasia for over 5 years has been reported) [44], even after the loss of circulating CD19 CAR-T-cells [45]. In the pivotal study of tisagenlecleucel, most patients received IGRT [1], whereas in a real-world study, 52.5% (134 out of 255) had hypogammaglobulinemia and 48.6% (124 out of 255) received IGRT [46].

Considering that BCMA is expressed in all plasma cells, it is not surprising that hypogammaglobulinemia is generally more frequently reported in BCMA CAR-T-cell therapy recipients. In a study of 55 adults with relapsed refractory multiple myeloma, severe hypogammaglobulinemia (IgG <300 mg/dL) was present in 42% of the individuals prior to lymphodepleting chemotherapy, in 70% between the first and third month post CAR-T-cell infusion, and in 41% at 1 year, and 58% received at least one dose of IGRT [38]. In an analysis of 32 patients, hypogammaglobulinemia (<400 mg/dL) was reported in 88% before BCMA CAR-T-cell therapy and in all patients after CAR-T-cell infusion [47]. While the pivotal BCMA CAR-T-cell trial reported post-CAR-T-cell hypogammaglobulinemia in only 21% of patients, IGRT was administered in 62% of the patients [6]. A summary of the proportion of patients with hypogammaglobulinemia and/or IGRT in pivotal and additional CAR-T-cell therapy studies is presented in Tables 1 and 2.

2.2. IgA and IgM

Data on IgA and IgM levels before and after CD19 CAR-T-cell infusion are scarce and typically reported in the context of low serum IgG levels. In a multi-center 'real-world' trial of the CD19-targeted CAR-T-cell product tisagenlecleucel in patients with large B-cell lymphoma, pre-existing low levels of IgG, IgA, and IgM were common and reported in 74%, 49%, and 63% of the patients, respectively, before infusion [2]. Of note, 96% of the patients had a history of rituximab-based therapies before entering the study. Among 10 adults with durable responses after tisagenlecleucel who did not receive IGRT, IgG, IgM, and IgA levels improved in 4, 6, and 3 patients, respectively, by ≥6 months after infusion (18 months or later for IgA levels)

Table 1. Infections, hypogammaglobulinemia and immunoglobulin replacement therapy (IGRT) in pivotal studies of commercially available CD19 and BCMA CAR-T-cells.

Study	CAR-T-cell product	Malignancy	Median time of FUP	Proportion of patients with infections ≥ grade 3	Proportion of patients with hypogammaglobulinemia	IGRT
Maude 2018 [1] (n = 75, children and young adults ≤ 21 years) ELIANA	Tisa-cel	B-ALL	13.1 m	24% by 8 weeks (any grade 43%)	NR	'most'
Schuster 2019 [2] (n = 111, adults) JULIET	Tisa-cel	DLBCL	14 m	20% by a median of 14 months (any grade 34%)	74% pre-CTI NR post-CTI	NR
Locke 2019 [48] Neelapu 2017 [3] (n = 108, adults) ZUMA-1	Axi-cel	DLBCL PMBCL Transformed FL	27.1 m	28% by 2 years	NR	31% overall; 8% between CTI and discharge; 44% with ongoing response
Abramson 2020 [4] (n = 269, adults) TRANSCEND NHL 001	Liso-cel	DLBCL High-grade BCL PMBCL FL grade 3B	18.8 m	12% by a median of 18.8 months Bacterial in 4%, viral in 1%, fungal in 1% of patients	14% post-CTI	NR
Wang 2020 [5] (n = 68 adults) ZUMA-2	Brex-cel	MCL	12.3 m	32% by a median of 13.2 months (any grade 38%)	Grade 3 in 1% post-CTI	32%
Munshi 2021 [6] (n = 128, adults) KarMMa	Ide-cel	MM	13.3 m	22% by a median of 13.3 months (any grade 69%) Bacterial in 23, viral 41, fungal in 11, unspecified in 82 patients	21% post-CTI (≥ Grade 3 in 1 patient)	62%

ALL: acute lymphoblastic leukemia; Axi-cel: axicabtagene ciloleucel; BCL: B-cell lymphoma; Brex-cel: brexucabtagene autoleucel; CTI: CAR-T-cell infusion; DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; FUP: follow-up; Ide-cel: idecabtagene vicleucel; IGRT: Immunoglobulin replacement therapy; Liso-cel: lisocabtagene maraleucel; MCL: mantle-cell lymphoma; MM: multiple myeloma; NR: not reported; PMBCL: primary mediastinal B cell lymphoma; Tisa-cel: tisagenlecleucel.

Table 2. Infections, hypogammaglobulinemia, and immunoglobulin replacement therapy (IGRT) in studies of commercially available and investigational CD19 CAR-T-cells.

Study	CAR-T-cell product and/ or malignancy	Time in months (m)	Incidence of infections	Type of infection (% of total events)	Risk factors for infection	Proportion of patients with hypogammaglobulinemia[1]/ IGRT	Association of hypogamma-globulinemia with infection
Commercial CD19 CAR-T-cells							
Logue 2020 [31] (n = 85)	Axi-cel/ NHL	0–1 1–12	37% (31/85) 44% (31/70)	Bacterial 52% (CDI 19%) Viral 44% Fungal 3%	• CRS • ICANS • Tocilizumab • Corticosteroids • Bridging Tx[2]	Pre-CTI: 28% (16/58) Post-CTI: 47% (8/17) by 1 year IGRT: 27%	No
Baird 2021 [29] (n = 41)	Axi-cel/ NHL	0–1 1–6 6-12 ≥12	46% (19/41) 40% (16/40) 43% (10/23) 47% (8/17)	Bacterial 40% Viral 37% Fungal 23%	• Corticosteroids	Pre-CTI: 10% (4/41) Post-CTI: 62% (23/37) during FUP IGRT: 37%	No
Strati 2021 [54] (***n*** = 31)	Axi-cel/ NHL	0–24	77% (24/31)	Bacterial 32% Viral 55% Fungal 13%[3]	• Grade 3–4 D30 lymphopenia[2]	Post-CTI: 46% (6/13) at 1 year, 44% (4/9) at 2 years IGRT: 55%	No
Wudhikarn 2020 [40] (n = 60)	Axi-cel, Tisa-cel/ DLBCL	0–1 >1 (median 6)	Cumulative incidence 1 year 63%*	Bacterial 68% Viral 27% Fungal 3% Protozoal 3% Bacterial 55% Viral 44% Fungal 2%	• Corticosteroids	Pre-CTI: 25% (15/59) **Post-CTI**: 44% (14/32) on day 30, 38% (12/32) after day 30 IGRT: 32%	Increased risk for viral infection HR 5.7 (95%CI, 2.3–14.3)[4]
Beyar-Katz 2021 [53] (n = 60)	Axi-cel, Tisa-cel/ DLBCL	0–1	45% (27/60)	Bacterial in 16p. Viral in 14 p. (CMV in 10, COVID-9 in 1)	• ICANS[2]	Post-CTI: 29% (9/31) on day 30	No
Investigational CAR-T-cells							
Hill 2018 [20] (n = 133)	ALL (35%) CLL (18%) NHL (47%)	0–1 1–3	23% (30/133) 14% (17/119)	Bacterial 56% Viral 30% Fungal 14% Bacterial 35% Viral 57% Fungal 9%	• ALL • ≥ 4 regimens • higher CAR-T-cell dose • CRS severity	Pre-CTI: 26% (34/133) Post-CTI: 35% (23/65) days 15–30, 27% (9/33) days 31–60, 46% (17/37) days 61–90	No
Zhu 2021 [52] (n = 92[5])	ALL (63%) NHL (37%)	0–1 1–6	12% 6%	Bacterial 80% Viral 10% Fungal 10% Bacterial 33% Viral 33% Fungal 33%	• Neutropenia pre-CTI • Prior infection • Corticosteroids for CRS	Pre-CTI: 32% (36/113)	No
Park 2018 [21] (n = 53)	ALL	0–1 1–6	42% (22/53) 31% (10/32)	Bacterial 65% Viral 19% Fungal 15% Bacterial 33% Viral 60% Fungal 7%	• CRS ≥ 3	Post-CTI: 83% (20/24) between days 31–180	No
Vora 2020 [39] (n = 83)	ALL (98%)	0–1 1–3	40% (33/83) 23% (11/48)	Bacterial 54% Viral 43% Fungal 3% Bacterial 42% Viral 58%	• Hypogammaglobulinemia • HCT • LD regimen	Pre-CTI: 16% (13/98) Post-CTI: 14% (11/78) on day 21, 29% (16/56) on day 63	Increased risk HR 2.41 (95%CI, 1.02–5.69) *Hypogamma-globulinemia post-CTI*

(*Continued*)

Table 2. (Continued).

Study	CAR-T-cell product and/or malignancy	Time in months (m)	Incidence of infections	Type of infection (% of total events)	Risk factors for infection	Proportion of patients with hypogammaglobulinemia[1]/ IGRT	Association of hypogammaglobulinemia with infection
Cordeiro 2020 [41] (n = 86)	ALL (30%) CLL (20%) NHL (50%)	>3 (min 12)	61% (33/54)	Bacterial 60% Viral 31% Fungal 9%	NR	Pre-CTI: 40% (34/86) Post-CTI: 67% (28/42) during FUP	NR

ALL: acute lymphoblastic leukemia; Axi-cel: axicabtagene autoleucel; CDI: *Clostridioides difficile* infection; CRS: cytokine release syndrome, CTI: CAR-T-cell infusion, DLBCL: diffuse large B-cell lymphoma, FUP: follow-up, HCT: hematopoietic cell transplantation, ICANS: immune effector cell-associated neurotoxicity syndrome; IGRT: immunoglobulin replacement therapy; LD: lymphodepleting chemotherapy, NHL: non-Hodgkin lymphoma, NR: not reported. Tisa-cel: tisagenlecleucel; Tx: therapy.

1: Hypogammaglobulinemia refers to IgG levels < 400 mg/dl in the studies by Hill, Vora, Logue, Baird, Wudhikarn, Beyar-Katz; IgG levels < 400 mg/dl and/or IVIG replacement in the study by Cordeiro, and < 600 mg/dl in the studies by Zhu, Park, and Strati.

2: No multivariate analysis performed.

3: 71 infection events: 17 viral, 10 bacterial, and 4 fungal while 50/71 non microbiologically documented. Percentages refer to only microbiologically documented infections.

4: IGRT did not decrease the incidence of infection.

5: 113 CAR-T-cell infusions in 92 patients (incidence calculated by authors using the total number of CTI).

*Cumulative incidence is reported when the number of patients who developed infections and the number of patients with available data are not reported.

despite molecular evidence of CAR-T-cell persistence; recovery of normal IgM and IgA levels occurred in 4 patients at 12–24 months from infusion, and 2 patients at 24 and 30 months, respectively [49]. In children and young adults with B-ALL, IgM and IgA levels progressively declined in all patients, and became undetectable in 71% of the patients at 71 days and 13% at 185 days, respectively [45]. The authors conclude that production of IgA is less impaired after CAR-T-cell therapy, in part due to the longer half-life of the IgA-producing long-lived plasma cells (usually years) compared to IgM-producing plasma cells (from weeks to months) [45]. Although the impact of low IgM or IgA levels on infection in CAR-T-cell recipients is not known, IgA and IgM levels at baseline did not differ between patients who developed infection and those who did not in one report, though specific analysis was not conducted [31]. IgM and IgA can be valuable surrogates for immune-reconstitution following CAR-T-cell therapy, especially in the presence of IGRT rendering IgG evaluation less helpful. These metrics are sometimes included in clinical decision-making regarding infection prevention strategies [50].

3. Pathogen-specific antibody deficiencies after CAR-T-cell therapy

Despite low total IgG levels, pathogen-specific immunoglobulin G (IgG) levels seem to be at least partially maintained following CD19 CAR-T-cell therapy. Compared to pre-CAR-T-cell concentrations, levels of IgG against measles were shown to be stable after CD19 therapy, and pathogen-specific IgG against tetanus toxin, Epstein–Barr virus, varicella zoster virus, and herpes simplex virus decreased but were still present [29,31,42]. Among the 30 individuals with complete remission following CD19 CAR-T-cell therapy, the proportion of participants with seroprotective IgG titers to vaccine-preventable infections was generally comparable to population-based seroprevalence data without re-vaccination [32]. However, seroprevalence for certain pathogens, such as *S. pneumoniae* and *H. influenza* type b was low, indicating gaps in protection. Importantly, pathogen-specific seropositivity did not correlate with total IgG levels, indicating some humoral protection in CD19 CAR-T-cell recipients despite hypogammaglobulinemia [32]. In contrast, a small cross-sectional study demonstrated that four BCMA CAR-T-cell recipients were half as likely to have seroprotective IgG titers to vaccine-preventable infections when compared to CD19 CAR-T-cell recipients [32]. However, depletion of long-lived plasma cells may occur even before BCMA CAR-T-cell therapy. This was illustrated in a longitudinal study that reported that measle-specific IgG were present in only five of 32 (16%) of patients with multiple myeloma before CAR-T-cell therapy, four of whom subsequently 'lost' their antibodies after therapy [47]. It is important to consider that children who received CD19 CAR-T-cell therapy potentially also have limited pathogen-specific antibody titers and spectra due to limited pre-established plasma cells prior to CAR-T-cell therapy, but more data are needed in this population [51].

In summary, prolonged hypogammaglobulinemia is frequent following CAR-T-cell therapies, and while there is growing evidence of at least partially maintained pathogen-specific IgG levels following CD19 but not BCMA CAR-T-cell therapy, seroprevalence for some critical pathogens seems to be generally low and memory B-cell pools may need to be re-established independent of CAR-T-cell type [32].

4. Infectious complications following CAR-T-cell-therapy

4.1. Epidemiology of, and risk factors for infection after CD19 CAR-T-cell therapy

Infections are a major complication after CAR-T-cell therapy, and are associated with a decrease in 2-year survival [52]. Clinical evidence on infectious complications following CD19 CAR-T-cell therapy is rapidly accumulating, though data are still limited in pediatric populations and in the long-term follow-up setting. Moreover, the retrospective, single-center design of many studies and the heterogeneity in patients' characteristics and preventive practices hinder critical analyses of their results. In pivotal clinical trials, infections grade ≥3 were reported in 10–32% of the patients following CD19 CAR-T-cell therapy, although fatal infections were extremely rare [1–5] (Table 1). Cohort studies evaluating infectious complications after CD19 CAR-T-cell therapy report an infection incidence of 23–46% within the first month following CAR-T-cell infusion and a subsequent decrease during the following months [20,21,29,31,39,40,52,53] (Table 2). While a direct comparison between studies is hindered by different time intervals, infection reporting and assessment methods, infections occur in 14–23% of patients between 1 and 3 months [20,39], 6–40% between months 1–6 months [21,29,52], and in approximately 40% of the patients over the course of a year after CAR-T-cell therapy [31]. Infections occur in almost 50% of all patients after 12 months [29], and in 77% of the patients during a 2-year follow-up [54]. Finally, late infections, occurring beyond 90 days, were reported in 61% of the patients who had at least 1 year of follow-up (median duration of follow-up 28.1 months, range: 12.5–62.6) [41].

Bacterial infections predominate early after CAR-T-cell infusion, while viral infections, in particular respiratory viruses, account for most late infections [20,21,40,52,53] and fungal infections are reported in 5–10% of the patients [20,55], especially in the setting of prolonged neutropenia [22], prior HCT, and immunosuppressive therapy for CRS [15]. This pattern may vary in favor of more frequent viral infections in certain populations, such as children [39], adults with large B-cell lymphoma [29,31], or after BCMA CAR-T-cells [38]. By analogy with patients with primary immunodeficiencies, severe bacterial infections, especially of the sinopulmonary tract, would be the anticipated late events in the setting of prolonged hypogammaglobulinemia after CAR-T-cell therapy. In a study of late events (after 3 months) in patients with at least 12 months of follow-up, the most common infectious events were lower and upper respiratory tract infections (more than 70% of all infections); among microbiologically documented infections, 60% were bacterial, and when examining serious infections requiring hospital admission or ICU admission, bacterial causes

accounted for around 70% of all infections (73% hospital admission, 67% ICU). These findings confirm that even though respiratory viral infections are generally the most frequently reported late infections, serious bacterial infections, which are considered the hallmark of hypogammaglobulinemia, are also relevant during this period [41].

Reactivation of herpes viruses, particularly CMV reactivation, is increasingly being reported in this population [53]. Of note, PCR testing for CMV is not routinely performed in many centers without a clinical indication and/or the presence of major risk factors, such as additional immunosuppression with high-dose corticosteroids and anti-cytokine agents, and the true CMV incidence could be inaccurately estimated. Data on SARS-CoV-2 infection and related outcomes in CAR-T-cell recipients are scarce; according to a recently published study in 57 CAR-T-cell recipients, COVID-19 was associated with prolonged hospitalization and viral shedding and a high attributable mortality of 41% (median time from COVID-19 until death was 4.9 weeks, min-max: 1–21.6 weeks) which was calculated to be 10–40 times higher than in the general population of countries currently most affected by COVID-19 [56]. Another European study reports severe SARS-CoV-2 infection in 67% of patients, need for ICU admission in 43% and a COVID-19 attributable mortality of 33% among CAR-T-cell recipients [57].

A plethora of factors have been linked to increased risk of infection in different studies; the most commonly reported risk factors include CRS severity [20,21] and corticosteroid treatment [29,40,52]. The type of underlying malignancy (B-ALL [20]), the intensity, and type of previous antitumor treatments (≥4 regimens [20], HCT [39]), a higher dose of CAR-T-cells [20], the lymphodepleting regimen (other than cyclophosphamide/fludarabine) [39], nneutropenia,and infections prior to CAR-T-cell infusion [52] have all been associated with increased risk of infection after infusion in multivariate analyses. Of note, hypogammaglobulinemia (IgG level <400 mg/dl) has been found to be independently associated with infection in children and young adults in one study [39].

Even though rates and kinetics of hypogammaglobulinemia following CD19 CAR-T-cells are frequently reported, data on the association between hypogammaglobulinemia and infections are conflicting, and the clinical impact of IGRT warrants investigation in controlled trials. In adults, severe hypogammaglobulinemia (IgG < 400 mg/dl) and/or IGRT was the most common late adverse event (67%) in one study reporting late events (beyond 90 days) in 86 patients with a spectrum of B-cell malignancies who had at least 1 year of follow-up [41]. Although the effect of hypogammaglobulinemia on infection was not studied, the high rate of sinopulmonary infections in this cohort could provide some evidence of its potential role as a risk factor for infection [41]. Another study reports an association between hypogammaglobulinemia and increased risk of viral infections, and authors attribute this finding to preexisting depleted plasma cells and antibody repertoire. IGRT did not have any impact on the incidence of infection [40]. Finally, several studies failed to demonstrate an association between hypogammaglobulinemia (baseline or after CAR-T-cell infusion) and increased risk of infection [20,21,29,31,52–54]. Tables 1 and 2 provide a summary of infection rates, types, and risk factors as well as the presence of hypogammaglobulinemia and association with infection.

4.2. Epidemiology of, and risk factors for infection after BCMA CAR-T-cell cell therapy

Data on the infectious complications related to BCMA-targeted CAR T-cells are limited. In one study encompassing products with various targets (CD19, CD22, disialoganglioside, or BCMA) and a spectrum of underlying diseases (162 children and adults enrolled on five phase I CAR-T-cell trials), the highest rate of infections within the first month was reported in patients with multiple myeloma receiving BCMA CAR-T-cell therapy (9 out of 24 patients, 38%) [58]. Infections grade ≥ 3 occurred in 22% of the patients in the pivotal clinical trial [6], and are reported in over 50% of the patients in retrospective single-institution cohorts (up to 1-year post CART-T-cell infusion [38], and up to 6 months after infusion [47]).

Viral infections are consistently the most common infections after BCMA CAR-T-cell therapy [6,38,47] and may be even more common than with CD19 CAR-T-cells (53% vs 20% of all infections, $p = 0.002$) [59]. Bacterial infections are the second most frequently reported infections, while fungal infections are more rare [6,38,47] (viral: 53%, bacterial: 40% and fungal: 6% up to 1 year after infusion [38]). All viral infections were due to respiratory viruses in one study [38], whereas herpesvirus reactivations accounted for most viral infections in another study, with a third of them being attributed to CMV reactivation ($n = 6$, 3 asymptomatic) [60]. Of note, weekly PCR testing for CMV was part of the protocol. Based on these data, the authors recommend regular monitoring and strict preventive strategies for CMV [60].

Severe hypogammaglobulinemia is very frequent both prior to and after BCMA CAR-T-cell therapy as detailed above, but the association between hypogammaglobulinemia and excess risk of infection is not clear. Use of steroids and post CAR-T-cell hypogammaglobulinemia <600 mg/dl have been identified as risk factors for infection in one study [59]. Conversely, even though 60% of the infections occurred in patients with severe hypogammaglobulinemia (<300 mg/dl) at the time of infection, neither hypogammaglobulinemia nor the administration of IVIG had an impact on infection in another study [38].

5. IgG replacement therapy

When evaluating the epidemiology of infections in CAR-T-cell recipients, it is important to consider what role IGRT may have in mitigating these complications. IGRT has primarily been established as beneficial for preventing serious bacterial infections, especially with encapsulated bacteria in the setting of primary immunodeficiencies [61,62]. There is less evidence to support its use to prevent respiratory viral or other viral infections, which are most frequently reported beyond the first

month after CAR-T-cell therapy. Patients with hypogammaglobulinemia are at increased risk of sinopulmonary and other invasive bacterial infections, and immunoglobulin replacement is a very effective infection prevention strategy in patients with primary immune deficiencies, among other indications [61]. IGRT is less well established in hematologic malignancies, while a decrease in infections has been demonstrated in certain cancer populations, these benefits are not always reproduced in large randomized clinical trials. Moreover, IGRT has not been associated with reduced mortality in a meta-analysis of clinical trials of patients with lymphoproliferative diseases, predominantly CLL and MM, and in HCT recipients [63,64]. However, there is substantial heterogeneity in the duration of follow-up among trials, and a relatively short duration of follow-up in most studies is a potential limitation for this assessment. Based on the limited benefits and the reported risk for sinusoidal obstruction syndrome, thrombosis, infusion reactions, and possible interference with post-transplantation vaccination, the recent ASBMT *Choosing Wisely* initiative recommends against routine IGRT after HCT [37,50,61,65]. It is conceivable that infection prevention strategies after CAR-T-cell therapy could align with recommendations for patients with primary antibody deficiencies. Indeed, the invasive bacterial infections and respiratory infections commonly reported following CD19 and BCMA CAR-T-cells are the hallmarks of primary antibody deficiencies [62,66]. However, even though the pathophysiology and epidemiology of infectious complications after CAR-T-cells suggest a potential role for prophylactic IGRT, this indication has not yet been substantiated by clinical data.

The indication for prophylactic IGRT following CAR-T-cell therapy remains controversial since there are currently no clinical trials evaluating its efficacy, and existing studies often failed to show a direct association between hypogammaglobulinemia and increased infection incidence [29,31,50,52,54]. Moreover, conclusions from existing studies are complicated by major differences in patients' characteristics, CAR-T-cell products, lack of consistent reporting of and heterogeneity in IGRT practices in different centers. Approaches to management of hypogammaglobulinemia may need to be tailored according to CAR-T-cell target and age group for reasons detailed above, along with clinical factors such as history of prior infections.

Since evidence-based guidelines are not available for IgG replacement after CAR-T-cells, current best practice recommendations are based on expert opinion [15,50,67,68] and adapted from guidelines in other immunocompromised populations, such as patients with hematologic malignancies and primary humoral immune deficiencies [37,61,62,66]. As a result, there is substantial heterogeneity in clinical practice between centers [69]. There is a consensus that baseline IgG levels should be measured pre-CAR-T-cell therapy and at monthly intervals for at least three months after infusion. A threshold IgG level of 400 mg/dL is frequently used to initiate IgG replacement therapy, and this is generally considered the minimal trough level, which should be maintained within the first three months after CAR-T-cell infusion [50,67,68,70]. However, it is important to note that total IgG levels are not necessarily a reliable biomarker of humoral immune function and may not correlate with pathogen-specific antibody titers or the ability to mount a specific antibody response. Some experts recommend against routine IgG replacement therapy in adult CD19 CAR-T-cell therapy recipients in the absence of recurrent or serious bacterial infections [50,68]. Monthly administration in patients with severe hypogammaglobulinemia can be considered when feasible, although the risk–benefit ratio of this approach is not yet clearly defined. A history of serious and/or recurrent infections may be more relevant than a relatively arbitrarily defined laboratory result when deciding to initiate IGRT, but an empirical trial of IGRT may sometimes be required [37,50,61,62,66].

For BCMA-targeted CAR-T-cell recipients, the pathophysiology of plasma cell depletion, and evidence to date of the effects on pathogen-specific antibody depletion, may support a more liberal utilization of IGRT among those with severe hypogammaglobulinemia (i.e. <400 mg/dL) even in the absence of infection. Of note, serum protein electrophoresis should be used to distinguish between normal IgG and paraprotein in multiple myeloma patients.

Empiric immunoglobulin replacement following CD19 CAR-T-cell therapy is typically standard practice in pediatric patients with hypogammaglobulinemia [71]. Serial IgG monitoring is useful to guide supplementation in this setting, and higher target IgG levels have been recommended [44,72]. Indeed, immune recovery after CAR-T-cells can take several years [43–45,73], and preexisting antibody producing plasma cells may be fewer in the pediatric population [51]. Furthermore, hypogammaglobulinemia has been associated with an increased risk of infection in pediatric patients treated with CAR-T-cells in one study [39], and higher serum IgG levels were associated with lower rates of sinopulmonary infections in one other study [44], though the data are very limited. A proposed algorithm for IGRT is summarized in Figure 3.

Usual starting doses for intravenous immunoglobulins (IVIG) are 400 mg/kg every 3–4 weeks; for subcutaneous administration of IgG, 100–200 mg/kg every week is the typical dose [50,67,68]. Among patients receiving IGRT, there is no consensus on when to discontinue, although a trial off IGRT would be reasonable if adequate IgG levels are maintained for three consecutive months and in the absence of recurrent bacterial infections [50]. An adequate immune response to vaccine challenge and specific antibody titers (including IgG for *S. pneumoniae* serotypes, tetanus, and diphtheria) can be an indication of recovery of humoral immunocompetence and could help orient the clinician toward a trial off IGRT [37,50,61,74].

Despite the great advances in the manufacturing process greatly enhancing the safety of immunoglobulin products, acute adverse effects occur in up to 40% of the patients after IVIG infusion, although most are transient and non-life-threatening; nonetheless, severe infusion reactions can occur [75–77]. The flu-like symptoms account for more than 80% of immunoglobulin-induced adverse effects [78,79]. Headache, musculoskeletal pain, nausea, flushing, tachycardia, dyspnea, and pyrexia are all commonly reported mild adverse events, and are more frequent upon IVIG initiation [75]. True IgE-mediated hypersensitivity is extremely

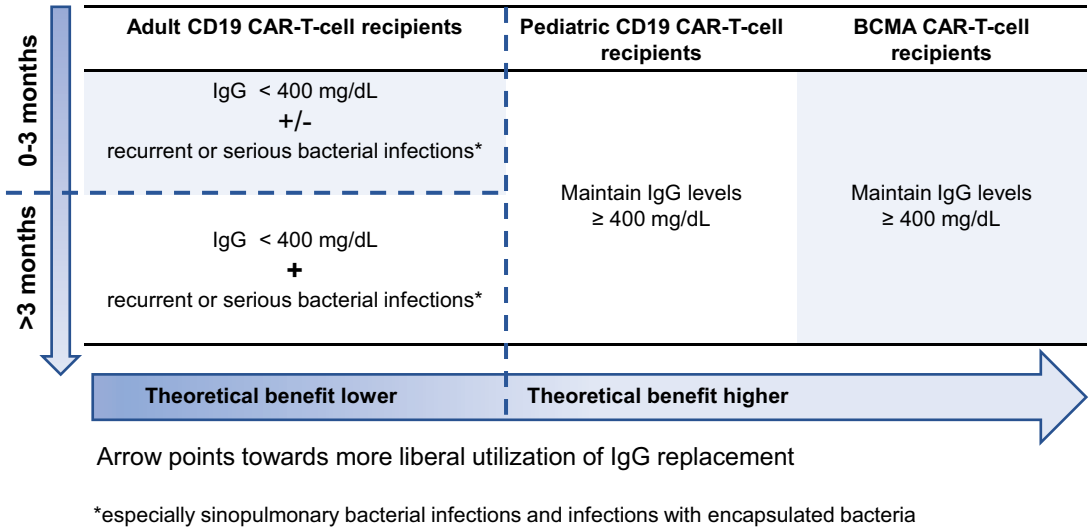

Figure 3. Proposed algorithm for IgG replacement in adult and pediatric patients treated with CD19 and BCMA CAR-T-cell therapy.

rare; however, anaphylactoid reactions are more common and result in similar clinical findings as anaphylaxis without the associated shock [50]. These reactions are frequently related to the rate of infusion and can be mitigated by pausing or decreasing the infusion rate, while premedication with NSAIDs and antihistamines could mitigate this risk.

Delayed adverse effects can be severe, but are extremely rare (1%) [78]. A black box warning is issued for all IgG products in the United States for the risk of thrombosis and renal failure. Estimates of the frequency of thromboembolic events vary with such events being reported in 1–17% of the patients, and arterial thromboembolic events are the most commonly reported (stroke, myocardial infarction, and pulmonary embolism) [80–82]. According to a large, population-based cohort of patients with hematologic malignancies (CLL or MM) the risk for myocardial infarction and ischemic stroke was transiently higher (three times higher) on the day of, and the day after IVIG infusion compared to matched controls with CLL and MM who did not receive IVIG [82]. Acute renal injury and failure have been mainly reported with IVIG containing sucrose as a stabilizer, which has been removed from most available IVIG products [83]. The exact incidence of renal injury, especially with newer formulations and lower doses of IVIG, is likely less than previously reported and there is a consensus that sucrose-containing products should be avoided in patients with impaired renal function. Furthermore, ensuring adequate hydration prior to administration, administrating IVIG at the minimum dose and infusion rate feasible and monitoring renal function, and for signs of thrombosis are indicated [50]. A transient mild hemolytic anemia due to isoagglutinins present in normal plasma pools used for IgG production can also occur in approximately 1.6% of the patients [84,85]. Finally, cost and access are important considerations, as these are very expensive and limited blood products. Careful stewardship of IVIG products to optimize use is thus of key importance, and clinical decision-making regarding IgG replacement therapy should be guided by multidisciplinary teams with the collaboration of onco-hematologists, immunologists, infectious disease physicians, and pharmacists [86].

Prospective controlled trials evaluating IgG replacement strategies after CAR-T-cell therapy are clearly needed to identify patient groups who would benefit the most from IgG replacement and inform evidence-based recommendations in this population. These studies will need to account for the differences in CAR-T-cell targets and patients' characteristics including age, hematologic malignancies, and prior treatment history. These results will be critical to determine efficacy and cost-effectiveness of IGRT.

6. Vaccination after CAR-T-cell therapy

Data on the immunogenicity and safety of vaccines in CAR-T-cell recipients are scarce. However, vaccination may be another key strategy for addressing pathogen-specific antibody deficits in this population. Furthermore, vaccination may allow patients to transition off IGRT and provide a more durable and cost-effective approach to infection prevention. However, vaccine responses may be lower than in healthy individuals because of ongoing B- and/or T-cell deficits.

Clinical practice for revaccination following CAR-T-cell therapy often follows protocols for HCT recipients. However, the need for revaccination for all previously completed vaccine series versus targeted vaccination for key pathogens, such as encapsulated organisms, remains unknown [15,67,87–89]. Based on the B-cell aplasia induced by CAR-T-cell therapies and the epidemiology of infections in this patient population, key vaccinations to consider include annual influenza vaccination and those targeting *Streptococcus pneumoniae, Haemophilus influenza* type b, *Corynebacterium diphtheriae* and *Clostridium tetani* toxins, *Bordetella pertussis*, and hepatitis A and B viruses. Vaccination for SARS-CoV-2 is currently recommended as early as 3 months after CAR-T-cell therapy, independent of prior vaccination history [90]. Measuring vaccine responses should be considered, and this may help to assess immune function and utility of additional vaccination [15,67]. A more detailed overview of possible approaches to vaccination and vaccine schedules is provided elsewhere [15].

The best timing of vaccination, either before or after CAR-T-cell therapy, is not well established. In general, delaying (re) vaccination with inactivated vaccines for at least 6 months after CAR-T-cell therapy is recommended to allow for immune reconstitution [15,67,68]. In CD19 CAR-T-cell therapy recipients, at least partial $CD19^+$ B-cell recovery is observed in some individuals around this time. This recommendation is also extrapolated from guidelines in patients treated with HCT or anti-CD20 therapy [87,91]. However, earlier vaccination as soon as 3 months can be considered in the setting of outbreaks with respiratory viruses such as influenza or SARS-CoV -2 [90,92]. Inactivated vaccines are not contraindicated following IGRT, and the Center for Disease Control and Prevention (CDC) does not recommend delaying COVID-19 vaccination for patients who received IGRT [91,93]. Live vaccines should generally be delayed for at least 1 year after CAR-T-cell therapy and deferred for several months after IGRT, which may interfere with viral replication and reduce vaccine efficacy [87,88,91].

Vaccination prior to CAR-T-cell therapy, as is established in solid organ transplant recipients, is appealing as it might induce long-lived plasma cell and T-cell responses that potentially could evade CD19 CAR-T-cell effects. However, vaccine immunogenicity in candidates for CAR-T-cell therapy is limited by a myriad of factors including active malignancy, recent receipt of high-dose chemotherapy, and B-cell depleting immunotherapies. Current guidelines for patients with hematologic malignancies recommend against vaccinating within 3–6 months after the end of the last anti-neoplastic therapy [88].

Although studies of vaccine immunogenicity before and after CAR-T-cell therapy are limited, they provide insights that can help guide clinical practice. A single study reported vaccine immunogenicity prior to CAR-T-cell therapy [94]: Of five individuals who received an inactivated influenza vaccine >2 weeks prior to CAR-T-cell infusion, two individuals (40%) with multiple myeloma demonstrated a ≥ 4-fold increase in antibody titers to at least one vaccine strain, and an additional individual with multiple myeloma had a ≥ 2-fold increase. Although titers decreased following CAR-T-cell infusion, they remained above baseline for at least 30 days after infusion, potentially providing some protection during this period of highest infection risk. Notably, these findings indicate the importance of repeating relevant vaccines after CAR-T-cell therapy, such as for SARS-CoV-2. Of the 13 CAR-T-cell recipients with oncologic remission who were vaccinated with the seasonal inactivated influenza vaccine >12 months after CAR-T-cell therapy, 77% had a ≥ 2 fold increase in antibody titers to at least one vaccine strain [94]. Notably, responses were observed in individuals with very low or no detectable $CD19^+$ B cells and individuals with severe hypogammaglobulinemia; most responders had IgA and IgM levels below the lower limit of normal. Similarly, Dhakal et al demonstrated an antibody response to the SARS-CoV-2 vaccine in 3 out of 14 (21%) CAR-T-cell recipients at 8, 24, and 31 months after CAR-T-cell therapy, and despite hypogammaglobulinemia in at least one of the responders [95]. Unfortunately, none of 7 individuals who received the SARS-CoV-2 vaccine prior to 6 months after CAR-T-cell therapy had evidence of an antibody response. In a study by Ram et al, 14 individuals were vaccinated with a SARS-CoV-2 vaccine 3–17 months after CAR-T-cell therapy; five individuals had detectable but low antibody response and six had evidence of cellular response, including three individuals with no antibody response [96].

These data demonstrate that patients can generate antibody responses to vaccines both prior to and after CAR-T-cell therapy, although responses tend to be lower than in healthy individuals, as expected. Responses appear to be reduced even in patients with long-term remission for years after CAR-T-cell therapy. However, hypogammaglobulinemia and CD19 B-cell aplasia do not clearly predict a lack of response to vaccination after CAR-T-cell therapy. Different expression patterns of CAR-T-cell targets in memory B-cells and plasma cells result in distinct humoral immune deficits following CD19 and BCMA CAR-T-cell therapy that will likely impact vaccine responses, so additional studies are clearly needed to better understand these nuances. The finding of reduced vaccine immunogenicity in CAR-T-cell recipients also underscores the importance of vaccination for caregivers and close contacts against vaccine-preventable infections.

7. Monoclonal antibodies in COVID-19

The increased severity and mortality of COVID-19 in CAR-T-cell recipients [56,57] in combination with the moderate immunogenicity of vaccines in this population [95,96], underscore an urgent need for additional preventive approaches in this setting. Neutralizing monoclonal antibodies targeting the SARS-CoV-2 spike protein, have been shown in clinical trials to reduce viral load, improve clinical outcomes (reduced progression to hospitalization, severe disease, death) [97,98] and prevent infection after exposure (household contacts) [99]. Several monoclonal antibodies have consequently been granted FDA emergency use authorization for the treatment of outpatients at high risk for severe disease (bamlanivimab/etesevimab, casirivimab/imdevimab, sotrovimab) [100–102], and for post-exposure prevention in patients who are not fully vaccinated or are not expected to mount an adequate immune response to the vaccine (bamlanivimab/etesevimab, casirivimab/imdevimab) [100,101]. More recently, in December 2021, emergency use authorization was issued for a combination of long-acting monoclonal antibodies, tixagevimab, and cilgavimab, for pre-exposure prophylaxis in high-risk patients. The product is administered as a single dose (two consecutive intramuscular injections) and provides protection for up to 6 months [103]. CAR-T-cell recipients are ideal candidates for both pre- and post-exposure prevention of SARS-CoV-2 infection due to their profound humoral immunodeficiency and increased risk of unfavorable outcomes of COVID-19. Importantly, monoclonal antibodies against SARS-CoV-2 provide a proof-of-concept for motivation for the development of additional pathogen-specific monoclonal antibodies to prevent other relevant bacterial or viral infections in individuals with severely impacted humoral immunity. Such monoclonal antibodies could be more efficacious than polyclonal antibodies in IVIG.

8. Antibiotic chemoprophylaxis

Long-term chemoprophylaxis is recommended in patients with active GVHD after allogeneic HCT due to increased susceptibility to recurrent bacterial infections with encapsulated bacteria such as *Streptococcus pneumoniae, Haemophilus influenzae,* and *Neisseria meningitidis* [104,105]. By analogy, antimicrobial chemoprophylaxis could be a promising strategy in hypogammaglobulinemic CAR-T-cell recipients at increased risk for recurrent bacterial infections with these pathogens. Indeed, trimethoprim/sulfamethoxazole is recommended for *Pneumocystis jirovecii* pneumonia prophylaxis for at least 6 months in CAR-T-cell recipients and is also active against most encapsulated bacteria, thus offering the inadvertent benefit of potentially preventing severe bacterial infections [15]. To what extent an antibacterial agent active against those pathogens (such as penicillin VK) should be added when trimethoprim/sulfamethoxazole cannot be administered is unclear.

9. Conclusion

CAR-T-cell therapy is associated with profound humoral immunodeficiency, but the attributable impact of hypogammaglobulinemia on risk for infection, and the best strategies for mitigating this risk, are not well understood. Differences in CAR-T-cell targets and 'on-target' 'off-tumor' side effects produce distinct humoral immune deficits that may warrant unique infection prevention approaches. Additional studies are needed to establish evidence-based strategies to mitigate the infectious risk related to antibody deficiency in CAR-T-cell therapy recipients.

10. Expert opinion

CAR-T-cell therapy is associated with profound humoral immunodeficiency, but the clinical significance of hypogammaglobulinemia remains incompletely understood. In the absence of clinical trials on infection prevention strategies after CAR-T-cells, clinicians must rely on extrapolations of recommendations developed in other contexts. Utilization of and access to commercially available CAR-T-cells continues to expand, highlighting that standardized infection prevention strategies are important to maximize the benefits of these potent treatments for our patients. Well-designed clinical trials will be an important next step to fulfill this unmet need for evidence-based guidelines but can be challenging due to the heterogeneity in patients' characteristics, CAR-T-cell products, and standard practices in different centers. Studies will also need to account for the distinct immune deficits seen with different CAR-T-cell targets.

Prophylactic IgG replacement therapy (IGRT) for hypogammaglobulinemia after CAR-T-cells has been considered standard of care, but this practice is not necessarily supported by clinical data. Total IgG levels may not be a good surrogate for risk stratification, although this is the main biomarker used to guide IGRT in typical practice algorithms and institutional recommendations. A thorough clinical assessment of patient's condition, immune reconstitution, and history of serious and recurrent bacterial infections, especially with encapsulated bacteria, are key elements in the decision-making regarding IgG replacement. Other criteria to consider include specific antibody titers and vaccine responses. It is possible that IGRT has limited benefit for preventing infections in adult CD19 CAR-T-cell therapy recipients based on accumulating evidence regarding the preservation of long-lived plasma cells, which can maintain specific antibody levels to previously encountered antigens. This might not be the case in children with fewer pre-established plasma cell clones and patients receiving BCMA-targeted CAR-T-cells. For now, careful stewardship of IGRT and individually tailored decision-making regarding its administration are needed.

Vaccination is an important component of infection prevention strategies in all immunocompromised patients, and CAR-T-cell recipients are no exception. However, concerns regarding weaker vaccine responses, especially early after infusion, are valid. The optimal timing of vaccination, and biomarkers to guide this decision, remain unclear. The COVID-19 pandemic has shed some light into vaccine responses in CAR-T-cell recipients, however data on the immunogenicity, safety, and practical aspects such as optimal timing after CAR-T-cell therapy are lacking. Prospective studies assessing efficacy and best timing are needed to inform evidence-based vaccination guidelines. The recently granted emergency used authorization of long-acting monoclonal antibodies for pre-exposure prevention of SARS-CoV-2 infection in patients who may not be able to mount adequate antibody responses to vaccines suggests an alternative preventive approach that could be particularly beneficial for CAR-T-cell recipients [103]. More importantly, these studies have laid the groundwork for the development of pathogen-specific monoclonal antibodies for other pathogens in the future. Finally, longer term antibiotic chemoprophylaxis for encapsulated bacteria, as indicated in patients with chronic active GVHD, needs evaluation in patients with delayed immune reconstitution and persistent hypogammaglobulinemia.

Identifying patients at highest risk of infection who might benefit from more intensive monitoring and infection mitigation strategies is a prerequisite to achieve the long-term objective of a more personalized management approach. Better tools for a sophisticated risk stratification to facilitate clinical decision making are on the way. Recently, a model including various biomarkers associated with hematopoietic reserve and inflammation was found to predict immune recovery after CAR-T-cells and identified patients at risk for prolonged neutropenia [18]. Such tools could also be adapted and used for infection risk assessment so that we can move towards data-driven assessments of infection risk and likelihood of benefit from more intensive prophylactic strategies.

Declaration of Interest

E Kampouri has received grants from the Swiss National Science Foundation (SNSF grant no. P500PM_202961) and SICPA Foundation. JA Hill received consulting fees or honoraria from Gilead Sciences. Amplyx, Allovir, Allogene therapeutics, CRISPR therapeutics, CSL Behring, OptumHealth, Octapharma, and Takeda and research funding from Takeda, Allovir, Karius, and Gilead Sciences. J Gauthier reports serving as a consultant for Eusapharma, JMP, Larvol, Multerra Bio, being in the advisory board of Legend Biotech and

Janssen and receiving research support from Sobi, Juno Therapeutics, and Celgene. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/iery20

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To cite this article: Lane H. Miller, Kim L. Maxa, Stuart S. Winter & Nathan P. Gossai (2023) The role of nelarabine in the treatment of T-cell acute lymphoblastic leukemia/lymphoma: challenges, opportunities, and future directions, Expert Review of Anticancer Therapy, 23:12, 1229-1236, DOI: 10.1080/14737140.2023.2271662

To link to this article: https://doi.org/10.1080/14737140.2023.2271662

EXPERT REVIEW OF ANTICANCER THERAPY
2023, VOL. 23, NO. 12, 1229–1236
https://doi.org/10.1080/14737140.2023.2271662

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DRUG PROFILE

The role of nelarabine in the treatment of T-cell acute lymphoblastic leukemia/lymphoma: challenges, opportunities, and future directions

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ABSTRACT

Introduction: Nelarabine is a guanine nucleoside analog and functions to terminate DNA synthesis in dividing cells. Pre-clinical and clinical studies have shown that it preferentially accumulates in T-cells where it exerts its cytotoxic effects. After generations of treatment protocol advances, it has been incorporated into numerous treatment regimens against T-lineage acute lymphoblastic leukemia/lymphoma (T-ALL/LLy). On 8 March 2023, the FDA approved the use of nelarabine for its use in T-ALL due to clear evidence of clinical benefits. This announcement concludes a nearly 6-decade period of evaluation for nelarabine and its role in the management of high-grade, aggressive T-cell malignancies.

Areas covered: We review the medicinal biology of nelarabine, its evaluation through decades of clinical studies, its dose-limited adverse effects, and its areas of highest impact in the treatment of T-ALL/LLy.

Expert opinion: We provide a context of when nelarabine might be considered in treatments against T-ALL/LLy, and also alternative strategies when it has or has not been used in therapies prior to relapse. We anticipate that an increasing number of treatment regimens will include nelarabine as a part of front-line therapy.

ARTICLE HISTORY
Received 22 July 2023
Accepted 12 October 2023

KEYWORDS
Nelarabine; T-cell acute lymphoblastic leukemia; T-cell acute lymphoblastic lymphoma; treatment; relapse; central nervous system; neurotoxicities

1. Introduction

1.1. The medicinal chemistry of nelarabine

The story of nelarabine began nearly 60 years ago, in the lab of Nobel Laureate Gertrude 'Trudy' B Elion in Raleigh, North Carolina [1]. In 1964, Elion and her colleague, George Hitchings, synthesized ara-G as a result of focused work on developing novel immunosuppressive drugs and observing subjects with purine nucleoside phosphorylase (PNP) deficiency, an inherited immunodeficiency disorder that results in severe T-cell deficiency. Unfortunately, ara-G lacked the chemical profile to become a successful drug given its poor water solubility and thus poor volume of distribution to tissues.

Yet, Elion persisted, determining that ara-G had a role in cancer treatment, brought ara-G back to the bench where she teamed up with colleagues to evaluate preclinical models both *in vitro* and *in vivo*, showing activity against human T-cell lymphoid malignancies. Elion was eventually able to overcome the chemical and pharmacokinetic challenges of ara-G to synthesize a pro-drug for ara-G with the addition of a methoxy group at the purine 6-carbon, compound 506U78 (known today as nelarabine) [2]. This compound had ten times the solubility of ara-G and was more apt to be a successful drug for clinical application [3,4]. With this development, the ability to mimic PNP deficiency state with ara-G, via its pro-drug nelarabine, resulted a pharmacologic agent with T-cell selectivity and ultimately T-cell destruction. Elion and her team then partnered with clinicians in 1994, when clinical trials of nelarabine began in humans. In 2005, the results of these clinical trials lead to the FDA approval of nelarabine with orphan drug status in 2005 [5].

In the United States, the FDA approved indication for nelarabine in 2005 (and still today) is for the treatment of adult and pediatric patients with T-cell acute lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LLy) aged 1 year and older whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens [6]. Since FDA approval, there have been numerous clinical trials utilizing nelarabine, of which eight are actively underway [See Table 1; Clinical trials.gov]. Additionally, with the recent U.S. patent expiration of the branded nelarabine product, Arranon beginning in 2021, generic nelarabine products have become available and will result in significant cost savings to patients and health systems, ultimately increasing patient access to this drug.

Nelarabine is similar in structure to its class of DNA nucleoside terminating agents, which include cytarabine, fludarabine, and clofarabine (See Figure 1) [7]. It is a cytotoxic agent with unique chemical and biological properties that have proven to be beneficial in the treatment of T-ALL/LLy. Nelarabine is a water-soluble prodrug of ara-G (9-B-arabinofuranosylguanine), a synthetic deoxyguanosine derivative that is resistant to cleavage by endogenous purine nucleoside phosphorylase. As a prodrug, in vivo, nelarabine primarily undergoes O-demethylation by adenosine deaminase to form Ara-G.

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Article highlights

- Nelarabine has proven to be both safe and efficacious in the treatment of T-lineage acute lymphoblastic leukemia.
- Nelarabine plays an important role in treating refractory disease and those with CNS3 leukemic involvement at diagnosis.
- Its adverse effects primarily include pancytopenia, immunocompromised, and neuropathies/myopathies that are largely reversible.
- Rarely, nelarabine can cause rhabdomyolysis and Guillain–Barré syndrome, which require its permanent discontinuation.

Pre-clinical studies in the early 1980s found ara-G to be cytotoxic to T-lymphoblasts at micromolar concentrations. Cytotoxicity arises from rapid conversion of nelarabine to ara-G by adenosine deaminase (ADA) upon administration, resulting in preferential accumulation of ara-G in T-lymphoblasts. As a result, phosphorylation of ara-G to ara-G triphosphate (ara-GTP), ara-GTP acts as an antimetabolite of the guanosine nucleotide blockade of DNA synthesis in T-lymphoblastic cells. This differential cytotoxicity between B-cells and T-cells has created interest in using this compound to treat T-cell malignancies (see overview for Figure 2).

Despite nelarabine's improved solubility from ara-G, it is still a difficult drug product to solubilize on a commercial scale. It is commercially available product in aqueous phase for direct intravenous administration and does not require further dilution prior to patient administration. Intravenous infusions of nelarabine are typically well tolerated with minimal to low emetogenicity. Close monitoring and supportive care should be emphasized in those patients with detectable or active disease who are at risk for tumor lysis syndrome, including adequate intravenous hydration and anti-hyperuricemic therapy in the hospital or hospital-based clinic. For patients who have tolerated prior cycles of nelarabine and have no detectable disease (e.g. during maintenance therapy), considerations can be made to administer nelarabine in the patient's home if appropriate resources and support are available, including patient access to homecare facility able to safely prepare and administer chemotherapy and patient's proximity to a hospital.

2. Results from phase 1, 2 and 3 clinical trials in children and adults

2.1. Phase 1 clinical studies

T-cell lymphoid malignancies have distinct biochemical, immunologic, and clinical features which set them apart from non-T-lymphoid malignancies [8,9]. Historically, the diagnosis of T-ALL portended a worse prognosis than other forms of non-T childhood ALL, calling for the development of therapies that were T-cell specific [10–12]. In a phase I study of Compound 506U78 in children and adults with refractory T-cell malignancies, a striking response rate was observed. Of 28 evaluable patients with T-ALL, there were 14 CR and 9 PR, with responses observed at all dose levels (5 mg/kg-75 mg/kg) [13]. Dose-limiting neurotoxicity consisting of weakness, ataxia, confusion, and coma was observed in 3 of 4 adults treated at the 60 mg/kg dose level, 2 of 31 adults treated at the 40 mg/kg dose level, and 1 of 11 children treated at the 60 mg/kg dose level. No neurotoxicity was observed in children treated at the 40 mg/kg level. The only child treated at the 75 mg/kg dose level experienced severe somnolence that resolved by day 10 but was followed by a generalized seizure on day 11 and was accompanied by ascending paralysis and coma. These symptoms persisted until the child died 10 weeks later from progressive leukemia. Thirty percent of the adults treated at a dose of 40 mg/kg have experienced reversible somnolence on day 6–7 after starting therapy with Compound 506U78.

2.2. Phase 2 clinical studies

Nelarabine was first used for children and young adults in a phase 2 clinical trial hosted by the Children's Oncology Group (COG) study P9673 for subjects who had suffered one or more relapses, or had progressive disease during induction therapy [14]. Surprisingly, among the 153 enrolled, evaluable participants, nearly half of the first relapse cohort entered into a second remission with single-agent therapy dosed at 650 mg/m^2, IV days 1–5. Similar results were seen for adults with relapsed T-ALL [15], but

Table 1. Active studies using nelarabine.

Title (recruiting, or active, not recruiting)	Centers	NCT
Multicenter Study of Risk-adapted Treatment for T-lineage ALL of Young Adults (18–59 Years Old) (GRAALL-2014/T)	Assistance Publique – Hôpitaux de Paris, France	NCT02619630
Everolimus in Combination With Nelarabine, Cyclophosphamide and Etoposide in Lymphoblastic Leukemia/Lymphoma (ENCERT)	Emory University – Atlanta, GA, USA	NCT03328104
Low-Intensity Chemotherapy and Venetoclax in Treating Patients With Relapsed or Refractory B- or T-Cell Acute Lymphoblastic Leukemia	M.D. Anderson Cancer Center, Houston, TX, USA	NCT03808610
Combination Chemotherapy and Nelarabine in Treating Patients With T-cell Acute Lymphoblastic Leukemia or Lymphoblastic Lymphoma	M.D. Anderson Cancer Center, Houston, TX	NCT00501826
Optimization of Therapy in Adult Patients With Newly Diagnosed Acute Lymphoblastic Leukemia or Lymphoblastic Lymphoma by Individualised, Targeted and Intensified Treatment (active, not recruiting)	Goethe University, Frankfurt, Germany	NCT02881086
Treatment of Newly Diagnosed Acute Lymphoblastic Leukemia in Children and Adolescents (active, not recruiting)	Dana-Farber Cancer Institute, Boston, MA, USA	NCT03020030
ALL-T19 study conducted by Japan Children's Cancer Group and Japan Adult Leukemia	• Lymphoblastic Leukemia • Japanese Pediatric Leukemia/ Lymphoma Study Group	JRCTs041210054

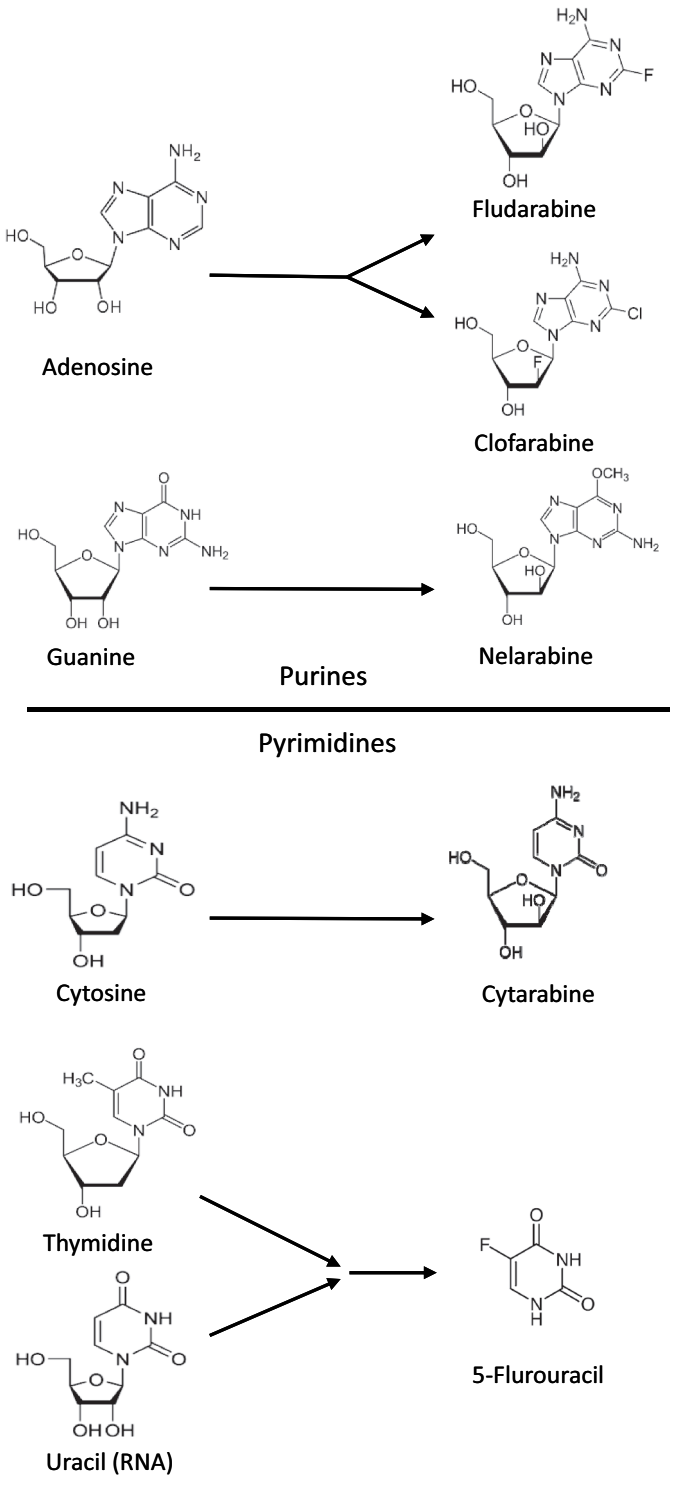

Figure 1. Nucleosides and selected nucleoside analogs used in anti-Cancer therapies. Nelarabine is a purine nucleoside analog for guanine. In contrast, cytarabine is a pyrimidine nucleoside analog for cytosine. While this class of drugs has a variety of drug-specific medicinal chemistries and related toxicities, most cause hematological adverse effects that commonly include pancytopenia.

using a dosing regimen 1.5 gm/m^2, IV days 1, 3, and 5 weekly. In some cases, the use of nelarabine allowed patients to proceed to successful allogeneic hematopoietic stem cell transplantation (alloHSCT). In addition to the expected adverse events associated with DNA nucleoside terminating agents, to include nausea and vomiting, myeloid suppression and chemotherapy-induced immunosuppression, nelarabine again caused some patients to have significant peripheral and central neuropathies, and more rarely, rhabdomyolysis [16].

Because of the overall positive results of the P9673 Phase 2 study, the COG supported a Phase 2 study that incorporated nelarabine into a COG-modified BFM backbone, entitled AALL00P2: The use of Modified BFM with or without nelarabine in an Intensive Chemotherapy Regimen for the Treatment of T-cell Leukemia [17]. This study again showed that the inclusion of nelarabine resulted in superior event free survival (EFS) and overall survival (OS) compared to participants who did not receive nelarabine, and that the adverse effects of nelarabine were manageable within the context of multi-agent therapy.

2.3. Phase 3 clinical studies

Building on the successful results of the AALL00P2 study, the COG next conducted a Phase 3 study in 1,895 subjects with T-ALL or T-lymphoblastic lymphoma (T-LLy), ages 1–31 years of age. A 2 × 2 randomization was used, in which patients received either Capizzi-style methotrexate versus high-dose methotrexate during the study's only interim maintenance phase, and to either receive or not to receive six 5-day courses of nelarabine, twice during consolidation, once during delayed intensification and three times during each of the first three maintenance phase cycles [8,18]. The study was powered to evaluate efficacy in the T-cell leukemia cohort, but not the T-LLy cohort, which was added to the study while it was in progress, largely because so many patients had lymphomatous disease, but not actual leukemia (an M3 marrow at diagnosis, defined by >25% bone marrow blasts).

In this large Phase III study of newly-diagnosed patients, the expected adverse effects of nelarabine were again observed, but not to the degree seen in the highly pretreated patients who were enrolled in earlier trials. The most common hematological abnormalities identified from the AALL0434 study were drug-related neutropenia and delayed platelet recovery. As was observed in several preceding instances, several patients developed drug-related rhabdomyolysis [16], with recommendations to not re-expose affected patients to nelarabine at any further point in therapy. Most Grade I to IV myopathies and neuropathies resolved during the later maintenance phases of therapy [8]. Two of 43 patients for who induction failed suffered Grade 5 neurological events that were attributable to nelarabine; however, EFS and OS for this subset of patients was approximately 50%, a percentage that was significantly higher than observed with prior therapeutic approaches that did not include nelarabine [18].

The Japan Children's Cancer Group and Japan Adult Leukemia Study Group recently published the results of their phase II studying incorporating nelarabine onto Associazione Italiana di Ematologia Oncologia Pediatrica (AIEOP)-BFM-ALL 2000-backbone with similar dosing of nelarabine to the COG with further encouraging results with 3-year EFS was 86.4% (95% CI 82.3–89.7%) and 3-year OS was 91.3% (87.7–93.8%) [19,20]. Further, this study did combine nelarabine with

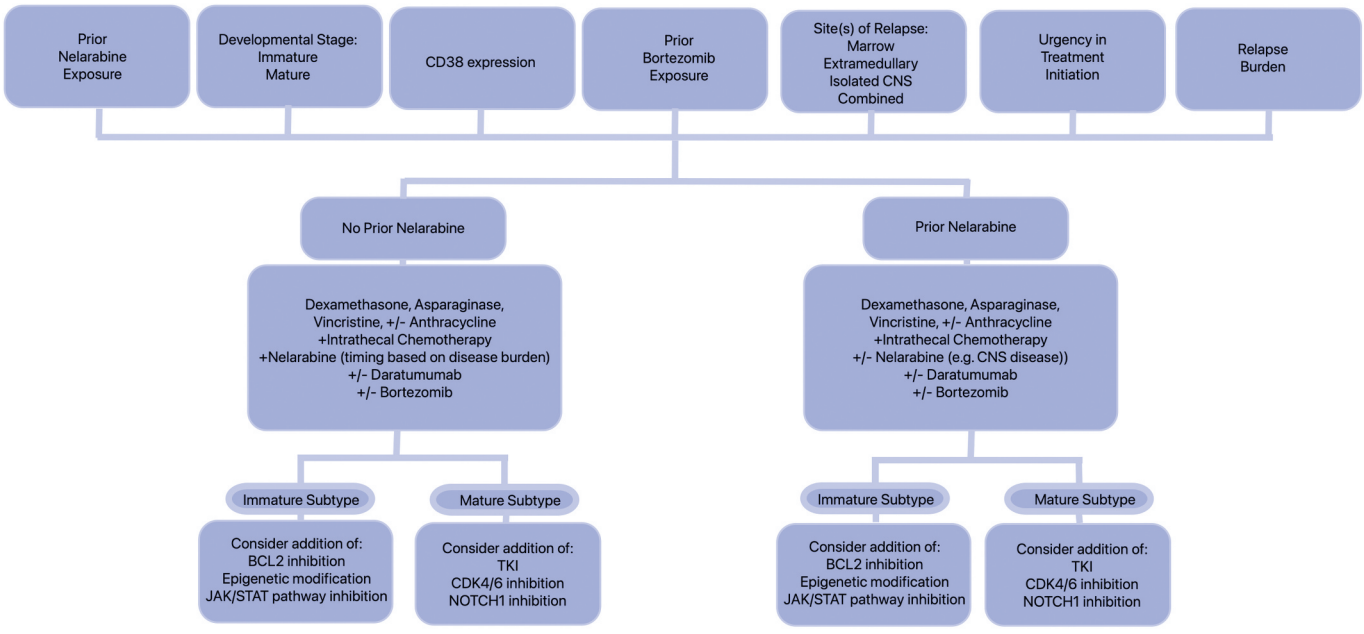

Figure 2. A treatment decision algorithm for second-line T-ALL/T-LLy therapy. In general, we recommend a steroid, asparaginase, and vinca alkaloid, with or without anthracycline in a re-induction backbone that incorporates additional agents based on a variety of factors including.

HD-MTX as no COG study has thus far done, with similar safety profile and outcomes.

3. Nelarabine improves survival for patients having high-risk features

3.1. Improvements in overall disease-free survival

As described above, the AALL0434 was a Children's Oncology Group (COG) phase III study for T-ALL and T-LLy patients, enrolling 1562 T-ALL patients from the years 2007–2014. Nelarabine was found to improve disease-free survival for children and young adults with T-ALL [18]. Specifically, the best outcomes were noted in the C-MTX-with-nelarabine treatment arm with 5-year disease free survival of 91% ($n = 147$). Further, nelarabine led to fewer isolated central nervous system (CNS) and combined CNS and bone marrow relapses (1.3% ± 0.63% vs. 6.9% ± 1.4%, $p = 0.0001$). No additional statistically distinct toxicities were noted on the nelarabine arms of therapy.

Of note, on AALL0434, protections for central nervous system disease were in place, thus CNS-3 patients were nonrandomly assigned to receive HD-MTX. Thus, none of the CNS-3 patients received the superior C-MTX therapy. One of the surmised benefits of C-MTX arms on AALL0434 was the early introduction of cranial radiation therapy and nelarabine in consolidation, consistent with the belief that early and intensive central nervous system consolidation may be contributing to decreased central nervous system relapse.

AALL0434 also enrolled 299 patients with T-LLy, who also fully participated in the nelarabine randomization. Nelarabine did not demonstrate improved outcomes in T-LLy patients, but the study was not powered to illuminate a benefit. Thus, in the recent report of T-LLy outcomes, the study committee proposed that nelarabine may still be active and worthy of incorporation into T-LLy therapeutic trials given the proven benefit in T-ALL patients, and the safety demonstrated in AALL0434 [19].

3.2. Specific nelarabine benefit for CNS disease in T-ALL patients

With decreased CNS relapses in T-ALL patients, a signal of nelarabine benefit stimulated further investigation that demonstrated that nelarabine has significant benefit for CNS-3 patients specifically. CNS-3 classification is the highest identified level of leukemia in the central nervous system. The benefit was large enough that CNS-3 outcomes were statistically similar to CNS-1 and CNS-2 patients receiving similar therapy [21]. Specifically, on the most successful treatment arm of AALL0434, disease free survival for CNS-3 T-ALL patients treated with HD-MTX and nelarabine at 4 years was 93.1% ± 5.2%. In contrast, patients treated with HD-MTX without nelarabine had 4-year DFS of 70.2% ± 5.8% ($p = 0.0151$) [21]. This success was starkly contrasted with the remainder of CNS-3 patients on AALL0434 who did not receive nelarabine and whose outcomes continue to be unacceptably poor. Those poor outcomes are illuminated by the increased cumulative incidence of relapse and decreased event free survival and overall survival for CNS-3 patients. As described above, T-ALL patients have not been treated with the superior C-MTX regimen from AALL0434 in conjunction with nelarabine. There is speculation that this combination may diminish the need for cranial radiation therapy in T-ALL patients.

4. Current institutional practice guidelines

In our institution, the Cancer and Blood Disorders Center at Children's Minnesota, we have incorporated the use of the superior arms of the most recent COG T-ALL Phase III studies to develop our current treatment regimen. Our aBFM treatment course includes the customary induction-Consolidation-Interim Maintenance-Delayed Intensification-Maintenance phases. In induction, we incorporate dexamethasone and bortezomib as used in AALL1231 with vincristine, daunorubicin, asparaginase, and intrathecal chemotherapy [22]. We give two doses of peg-asparaginase or a single dose of cal-asparaginase depending on the patient's age. Nelarabine is included in the consolidation phase with two courses of 650 mg/m2/day given on days 1–5 and 43–47. The remainder of consolidation consists of the AALL0434 arm B treatment with cyclophosphamide, cytarabine, 6-mercaptopurine, vincristine, asparaginase as well as intrathecal chemotherapy [18]. In addition, for patients with CNS-3 disease who are over 5 years of age, we consider 1800cGy of cranial radiation therapy during consolidation. The use of an age cut off at 5 years is to optimize benefits on CNS disease while minimizing the deleterious effects of CRT on the young and developing brain [23,24]. Interim maintenance is comprised of AALL0434 Arm B therapy as well, with C-MTX, without leucovorin rescue and two doses of peg-asparaginase (or a single dose of calaspargase pegol) as well as vincristine and intrathecal methotrexate. The second course of nelarabine is incorporated within delayed intensification (DI) using the framework of AALL1231 arm B in the first half of DI and AALL0434 arm B for the second half. The nelarabine is again 650 mg/m^2/days 29–33 [18,22]. Maintenance cycles 1–3 include nelarabine 650 mg/m^2/days 29–33 each cycle. Our intention is to optimize the central nervous system therapy with systemic chemotherapy of dexamethasone, asparaginase, and nelarabine to abrogate the need for cranial radiation therapy. We expect that our therapeutic approach will be approximated by the upcoming COG phase III trial AALL2331.

5. Relapse strategies based upon prior nelarabine exposure as a pivot point

5.1. Relapsed/Refractory disease – no prior nelarabine exposure

Relapsed childhood T-ALL and T-LLy are extraordinarily difficult diseases to successfully treat; both have secondary remission rates that remain low despite the use of intensified therapies. Most, if not all long-term survivors require alloHSCT once in remission to achieve cure [18]. In this context, decisions on a re-induction plan largely hinge on whether the patient has been exposed to nelarabine or not in the previous therapy [25]. Additional agents such as daratumumab (CD38-directed monoclonal antibody), alemtuzumab (CD52-directed monoclonal antibody), venetoclax (BCL-2 inhibitor), navitoclax (BCL-XL and BCL-2 inhibitor), bortezomib (proteasome inhibitor), palbociclib (CDK4/6 inhibitor), ribociclib (CDK4/6 inhibitor), dasatinib (tyrosine kinase inhibitor), and ruxolitinib (tyrosine kinase inhibitor) have also demonstrated promising single agent and combination efficacy in heavily pretreated relapsed disease [23,24,26] and are seldom incorporated into front-line T-ALL/T-LLy protocols thus far. Moreover, chimeric antigen receptor (CAR) T-cell therapy is evolving as a potential option. In general, bearing in mind the extremely poor prognosis associated with relapsed/refractory T-cell ALL/T-LLy, any of these investigational agents should be considered if available and felt to be reasonably effective and safe.

As described, nelarabine as a single agent has demonstrated noteworthy response rates in relapsed and refractory disease. A recent meta-analysis reported a pooled CR prevalence of 37% among 653 adult and pediatric subjects on 8 clinical trials [27], allowing many patients the opportunity to attempt curative alloHSCT. In regards to children specifically, a phase I multicenter study including 26 children with relapsed/refractory T-ALL/T-LLy receiving varying doses of nelarabine monotherapy resulted in a 42% CR + PR rate [28]. A similar phase I study including 70 children with relapsed/refractory T-ALL/T-LLy, also at a wide range of doses, achieved a 34% CR + CR rate [29]. As previously noted, the Children's Oncology Group conducted a phase 2 trial that treated 153 relapsed/refractory T-ALL/LLy patients <21 years of age with single-agent nelarabine at three dose levels. At the ultimately established 650 mg/m2 dose, responses included a 55% CR + PR rate in 34 T-ALL patients in first relapse, 27% CR + PR rate in 30 T-ALL patients in second relapse, and a 43% CR + PR rate in 7 T-LLy patients [14].

Additional benefit has been demonstrated when combining nelarabine with intensive chemotherapy in the relapsed and refractory setting. The NECTAR protocol treated seven pediatric relapsed/refractory T-ALL/T-LLy patients with nelarabine in combination with cyclophosphamide and etoposide, achieving five CRs (71.4%) and one long-term survivor [30]. The Dana-Farber Cancer Institute treated a larger cohort of 29 patients aged 2–69 years of age similarly with nelarabine, cyclophosphamide, and etoposide, yielding a 62% CR rate and a remarkable 53% 24-month OS, with most responders able to proceed to alloHSCT [31]. Additionally, nelarabine has been combined with daratumumab and chemotherapy in three adult cases [32,33] and venetoclax with or without chemotherapy in five adult cases [34,35].

5.2. Relapsed/Refractory disease – prior nelarabine exposure

For those relapsed patients who have been previously exposed to nelarabine during up-front therapy, regimens remain available using alternative agents, many of which have been noted earlier in this section. The utility of incorporating nelarabine in previously exposed relapsed/refractory patients is unclear at this point and could still be considered depending on the circumstances. Daratumumab, an anti-CD38 monoclonal antibody initially FDA approved for treatment of multiple myeloma, has been recently evaluated in the context of CD38 positive T-cell lymphoblastic disease. The phase 2 DELPHINUS study treated 39 children and young adults with T-ALL/LLy with daratumumab at 16 mg/kg weekly in

combination with dexamethasone, doxorubicin, asparaginase, and vincristine for cycle 1 and methotrexate, cyclophosphamide, cytarabine, and 6-mercaptopurine in cycle 2, yielding an ORR of 83.3%, including MRD negativity in 41.7% [36]. These outcomes were notably superior to being treated with these chemotherapy backbones on their own and the addition of daratumumab was well tolerated.

Additional agents have shown benefit depending on maturation subtype. Generally, T-ALL/LLy can be categorized based on the stage at which developmental arrest occurred, which can be gleaned based on the immunophenotype [37], genetic alterations, gene expression profile, and TCR rearrangements. The ETP, near-ETP, and additional subtypes have been well described [38] and can be categorized as 'immature,' which generally is characterized by fewer instances of TCR rearrangements, reduced *CDKN2A/B* and NOTCH1 aberrations, increased JAK/STAT pathway activation, and increased expression of epigenetic regulators ERG and LYL1. Alternatively, more 'mature' subtypes of T-ALL/T-LLy frequently demonstrate TCR rearrangements, CDKN2A/B deletions, NOTCH1 activating mutations, TAL/LMO overexpression, and ABL class rearrangements.

Immature T-ALL subtypes have demonstrated increased sensitivity to BCL2 inhibition [26]. A recent phase I dose escalation study in children and adults with relapsed/refractory T-ALL/T-LLy provided venetoclax and low-dose navitoclax in combination with dexamethasone, asparaginase, and vincristine, resulting in a 56% CR rate among heavily pretreated T-ALL patients [25]. In consideration of aberrant epigenetic regulation noted in immature T-ALL/T-LLy, extensive preclinical work has demonstrated potential benefit to DNA methylation and histone deacetylase inhibition in tumor suppression [36,39–41]. Ruxolitinib has also displayed efficacy in preclinical ETP-ALL models [42] with some anecdotal evidence of success in relapsed/refractory patients [43–48].

ABL1 class rearrangements have been frequently demonstrated in more mature T-ALL/T-LLy subtypes, particularly the NUP214-ABL1 rearrangement [36], although even in ABL1 negative mature T-cell disease, dasatinib has exhibited preclinical efficacy [23] along with a demonstrable anecdotal effect in patients [24].

As noted previously, while many of these medications are not yet FDA approved for the purpose of relapsed/refractory childhood T-ALL/T-LLy nor have early-phase trials extensively investigated their safety and efficacy in the suggested combinations, given the dismal prognosis associated with this disease, novel combinations could be considered while exercising great caution and engaging in shared decision-making with families. Certainly, eligible patients should be considered for open clinical trials where available. Moreover, the combination with any of these agents with nelarabine should be considered if the safety profile is felt to be tolerable, whether or not prior nelarabine exposure has occurred.

6. Expert opinion

The long path from chemical inquiry to pharmaceutical development to delivery to the patient is certainly non-traditional, but the introduction of nelarabine into pediatric leukemia practice has much promise and may help achieve the two primary and complementary objectives of clinical care, namely to increase the efficacy of treatment while avoiding untoward side effects. Nelarabine has improved care by improving survival in T-ALL patients and demonstrating a signal of benefit in T-LLy. Yet, notably, perhaps its largest impact on survival is demonstrated in those patients who need it most, those with high-risk disease and CNS-3 status. While its survival improvement is critical, nelarabine also led to lower incidence of relapse which prevents patients from requiring therapies of increasing intensity and toxicity. Further, the incorporation of nelarabine into treatment regimens, in concert with additional advancements, may abrogate the need for cranial radiation therapy in nearly all children, adolescents, and young adults with T-ALL and T-LLy.

We recommend that all newly diagnosed high-risk T-ALL patients, especially those with CNS-3 status, receive nelarabine as a portion of their treatment regimen. We encourage treatment teams to incorporate nelarabine into earlier phases of therapy as early intervention to prevent relapse is warranted in T-ALL. As outlined in our institutional treatment guideline, we initiate nelarabine therapy at the beginning of aBFM consolidation. Subsequent nelarabine is given in delayed intensification and maintenance. Further, we would incorporate nelarabine in to our treatment courses of new T-LLy patients as there is a signal of benefit and its safety has been established. We recommend that all relapsed T-ALL and T-LLy patients, if they have not received nelarabine as a component of their initial therapy, also receive nelarabine.

While nelarabine shows promise, caution must be taken to ensure safety in newly diagnosed, relapsed, and refractory disease. The timing of dosing should follow an initial induction or re-induction course to ensure that the disease burden has lessened as side effects with nelarabine are more prevalent and more significant with large leukemic burden. Our institutional goal is to initiate nelarabine with patients who have negative MRD or low MRD level detectable leukemia or lymphoma. While we attempt to provide complete dosing, we have limited dosing in patients where significant neuropathies have been noted. We can monitor and intervene with our adept physical therapy team. We have omitted doses for patients who have critical rhabdomyolysis. We have not observed central neuropathies or demyelinating disorders, but we monitor closely during nelarabine courses to assess for such events.

Much optimism surrounds the incorporation of nelarabine into clinical practice as we seek better outcomes and diminished toxicity for a population of T-cell patients. With attention to timing, dosing, and potential side effects to ensure safety, we believe nelarabine will become an essential component of future treatment regimens.

Funding

This paper was not funded.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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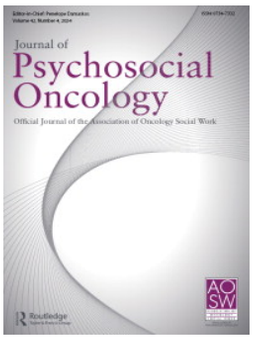

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Journal of Psychosocial Oncology

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/wjpo20

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To cite this article: Dorothy Leahy, Kelly E. Irwin, Gerd Murphy & Paul D'Alton (2024) Cancer care for people with significant mental health difficulties (SMHD) - patient perspectives, Journal of Psychosocial Oncology, 42:4, 506-525, DOI: 10.1080/07347332.2023.2291203

To link to this article: https://doi.org/10.1080/07347332.2023.2291203

Published online: 14 Dec 2023.

JOURNAL OF PSYCHOSOCIAL ONCOLOGY
2024, VOL. 42, NO. 4, 506–525
https://doi.org/10.1080/07347332.2023.2291203

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RESEARCH ARTICLE

Cancer care for people with significant mental health difficulties (SMHD) - patient perspectives

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ABSTRACT

Objectives: People with significant mental health difficulties (SMHD) experience inequities in cancer care. This study aims to deepen understanding of cancer care for individuals with SMHD.
Method: We conducted semi-structured interviews with seven individuals with SMHD regarding their experiences accessing and engaging with cancer care from August 2021 to February 2022. Data were analyzed using thematic analysis where both inductive and deductive coding was adopted through the lens of the socio-ecological model (SEM) as a theoretical framework.
Results: The main themes included intrapersonal, interpersonal and organizational barriers and facilitators to care with a specific focus on modifiable factors related to cancer care delivery.
Conclusion: This study provides further evidence for promoting collaborative mental health and cancer care delivery to prevent inequalities in cancer care for patients with SMHD.
Practice implications: Adopting an interdisciplinary, team-based approach to cancer care and help with patient navigation across services are potential factors in improving cancer care for individuals with SMHD.

KEYWORDS
cancer care; significant mental health difficulties

Introduction

Inequities in cancer care for patients with SMHD have resulted in cancer mortality rates that are two to four times higher among patients with SMHD compared to the general population.[1,2] In keeping with previous research in the field, individuals with SMHD include major depression, schizophrenia and bipolar disorder.[3,4] Previous research reported key contributors to delays and inequities in cancer screening and treatment for individuals with SMHD including: mental illness severity;[5] lack of adherence to cancer treatment;[6] fragmentation in the delivery of mental and physical healthcare[7–10] and clinician attitudes/stigma resulting in diagnostic overshadowing where patients' physical symptoms are minimized.[4,11,12]

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Previous qualitative studies based on the experiences of individuals with mental health difficulties accessing cancer care have reported: logistical barriers to care including transport issues;[13,14] financial difficulties; insufficient access to mental health services and childcare responsibilities.[13,15,16] Factors that facilitate care included: having screening conducted by a well-known healthcare professional;[14] appointment reminders; encouragement from family members and healthcare professionals.[13,14]

Our team recently conducted a qualitative systematic review which focused specifically on potentially modifiable barriers and facilitators that are unique to individuals with SMHD, six qualitative studies were identified based on 133 individuals with SMHD and 102 healthcare professionals regarding experiences and attitudes to accessing and engaging with cancer care. The key barriers to cancer care were related to patients' uncontrolled psychiatric symptoms and the associated adverse implications on engaging with care, stigmatizing attitudes from clinicians and other staff toward individuals with SMHD and fragmentation of mental health and cancer care delivery. The main facilitators to care included: being connected with mental health services; controlled psychiatric symptoms; stronger collaboration across healthcare services and the inclusion of a patient navigator/liaison staff member to facilitate patient engagement in their care.[17]

While barriers and facilitators in relation to patient, provider and system factors to accessing and engaging with cancer care for this specific patient population were identified in previous research; patient perspectives for this particularly marginalized population are lacking in the literature. The aim of this study is to investigate the experience of cancer care for individuals with SMHD from the person's perspective; in keeping with growing trends in Public and Patient Involvement (PPI), the inclusion of patient perspectives can only enhance the generation of in depth knowledge to inform future service provision.[18]

Methods

Study design

As the current study aimed to investigate the perspectives of participants with SMHD accessing and engaging with cancer care, a qualitative approach was adopted to facilitate a deeper understanding of participants' experiences. In the current study a constructivist paradigm was applied which involves a pluralistic, interpretive, open-ended, and contextualized (e.g. sensitive to place and situation) perspectives toward reality. In the constructivist paradigm, the ontological position is based on the idea that all truth is constructed by humans and situated within a historical moment and social context.[19] Multiple meanings exist of perhaps the same data

and the epistemological position suggests that the researcher and participants are linked, constructing knowledge together.[19] The importance of understanding the human experience in relation to social context was particularly relevant to the current research as the aim was to increase understanding of patients with preexisting SMHD in relation to their experiences of accessing cancer care. The Consolidated Criteria for Reporting Qualitative Research (COREQ) was used as a reporting framework for this study (Appendix A).

Conceptual framework

The socio-ecological model (SEM) was used as an underlying framework to guide the development of the interview schedule (Appendix B) and data analysis. The SEM has been applied as a theoretical framework across a wide range of studies to determine the various factors (individual, interpersonal, community/societal) that impact patients' interactions with healthcare services regarding perceived barriers and facilitators to chronic kidney disease,[20] colorectal cancer[21] and HIV testing.[22]

Participants

Participants were cancer patients across the trajectory of the disease with preexisting SMHD; all participants in the current study were either in the follow-up stages of cancer treatment or they had been discharged. Participants were eligible to participate if had they a preexisting SMHD (e.g. major depression, schizophrenia and bipolar disorder) and had a confirmed cancer diagnosis and had received cancer treatment (including surgery, radiation or chemotherapy). Participants were excluded if they had mild mental health difficulties and were under the age of 18 years. Psychiatric inpatients were excluded as requested by the Research Ethics Committee.

Two recruitment strategies were used: 1) participants were recruited through two hospitals in Ireland via psycho-oncology, psychiatry and outpatient clinics and 2) due to poor uptake from hospital recruitment, an ethics application was approved in November 2021 to recruit participants via online cancer and/or mental health support websites.

In keeping with guidelines from Braun and Clarke,[23] it was decided against calculating an estimated sample size for the purpose of data saturation, as the authors suggested that researchers should "dwell with uncertainty and recognize that meaning is generated through interpretation of, not excavated from, data, and therefore judgements about 'how many' data items, and when to stop data collection, are inescapably situated and subjective, and cannot be determined (wholly) in advance of analysis".[23]

Procedure

For hospital-based recruitment, the psychiatrist and/or advanced nurse practitioner from psycho-oncology/psychiatry assessed patient capacity to partake and consent in research. Participants received an invitation letter and a patient information sheet about the study at their clinic. For the online recruitment, mental health and/or cancer organizations were emailed to request permission to advertise the study on their websites. Following approval from the relevant organizations, a study advert was displayed on associated social media platforms. Prior to participating in the interview, participants provided written consent. A debrief sheet was provided with relevant support contacts following completion of the interview.

DL, who is a female psychologist in clinical training, with extensive experience conducting qualitative interviews conducted the interviews over the telephone due to COVID-19 restrictions; she was not involved in the patients' treatment.

Interviews used a semi-structured guide and lasted from 33 min to 2 h and 29 min (the mean interview time was 1 h and 10 min). Participants were offered breaks during the interview and had the option of conducting the interview over two sessions. The semi-structured approach enabled the researcher to focus on specific domains of the interview guide including initial help-seeking habits, cancer diagnosis and treatment, and follow-up, while also offering flexibility for data to emerge from lived experience. We aimed to provide flexibility to allow a population that is rarely given a voice the opportunity to be heard in a flexible way.

While approximately 20 study packs were distributed across both hospitals, only four participants contacted the researcher to participate in the study and one participant dropped out prior to participating in the interview. Seven participants followed up with the researcher from the online recruitment, however, three participants did not meet the study inclusion criteria where individuals did not have a diagnosed SMHD ($n = 2$) or their SMHD resulted from having from having a cancer diagnosis ($n = 1$).

Data analysis

Interviews were transcribed verbatim by DL. Transcripts were uploaded to NVivo 12, a qualitative data analysis software. Member checking was conducted where participants were invited to review their data and evaluate its accuracy. Data were analyzed per guidelines from Braun and Clarke.[24] To ensure inter-rater reliability, all transcripts were double coded by PD. Similar to previous qualitative studies, a hybrid approach was applied to the data analysis,[25,26] which balanced inductive and deductive coding. To address the main research questions, there was a two-step approach to data analysis, themes were analyzed inductively to allow for participants'

experiences to emerge from the data, for the second step, transcripts were analyzed through the lens of the SEM, where themes focussed on the main barriers and facilitators for people with SMHD to accessing and engaging with cancer care. Previous research that applied the SEM framework adopted a similar approach to analysis.[20]

The current study received ethical approval from St Vincent's University Hospital Ethics and Medical Research Committee (Ref No: RS18-045), the Research Ethics Committee, HSE, South East (no reference number provided), an exemption from full ethical review was granted by the UCD Office of Research Ethics (Ref No:LS-E-21-221-Leahy-Dalton) and ethical approval for online recruitment was obtained from the UCD Office of Research Ethics (Ref No: HS-21-67-Leahy-Dalton).

Results

Description of study participants

Seven participants (5 females and 2 males) with a history of SMHD and a subsequent diagnosis of cancer participated in semi-structured interviews from August 2021 to February 2022. Participants were recruited from two urban-based hospitals in Ireland ($n = 3$) and mental health and cancer support organizations via online recruitment ($n = 4$). Participants ranged in age from 37 to 62 years, with a mean age of 50 years. Three participants were married and three participants had children. Four participants were employed, and the other participants were retired ($n = 1$), on a disability payment ($n = 1$) and a stay-at-home parent ($n = 1$). Participants' diagnoses included: major depression (verified by their treating clinician where possible e.g. for participants recruited from hospital settings) ($n = 4$), mixed depression and anxiety ($n = 1$), borderline personality disorder and depression ($n = 1$), schizophrenia and depression ($n = 1$) and three participants also reported experiencing symptoms of anxiety. The number of years since participants received their mental health diagnoses ranged from 2 to 35 years and participants received their cancer diagnoses between 2014 and 2021. The participants' cancer diagnoses included: breast cancer ($n = 3$), ovarian cancer ($n = 1$), uterine cancer ($n = 1$), colorectal cancer ($n = 1$) and throat cancer ($n = 1$). The length of time participants were experiencing physical symptoms prior to seeking medical attention ranged from two days to seven months. Six out of the seven participants were taking psychotropic medication during their cancer treatment and five participants were seeing a psychiatrist. At the time of interview most participants ($n = 5$) were receiving follow-up care from cancer services; two participants had been discharged. Two participants had been discharged from psychiatric services, one participant was seeing a psychotherapist privately, two

participants were trying to access counseling through voluntary cancer organizations in their local area and two participants were engaged with psychiatry through local primary care teams.

Overview of themes

Themes were divided into the following areas in accordance with the SEM model; Intrapersonal (e.g. participants' attitudes, beliefs, knowledge, and behaviours); Interpersonal (e.g. families, friends, communication with healthcare professionals) and Organizational (e.g. relationships and communication between healthcare disciplines and organizations) barriers and facilitators. Table 1 provides an overview of the main themes and subthemes. For the purposes of the current paper, we have decided to focus on the most salient subthemes in relation to the main barriers and facilitators described by participants when accessing cancer care.

Theme 1: Intrapersonal barriers

Increased mental health symptoms during cancer care

Some participants reported a significant deterioration in their mental health following their cancer diagnosis, particularly in response to the pain and illness following chemotherapy treatment. In some cases, participants experienced thoughts about ending their life.

Table 1. Overview of main themes and subthemes.

Intrapersonal	Barriers • Increased mental health symptoms during cancer care • Additional psychosocial stressors during cancer care • Staying in survival mode as a way of coping	Facilitators • Utilizing coping strategies learned from mental health supports • Improved mental health following cancer diagnosis
Interpersonal	Barriers • Patients with SMHD found it difficult to advocate for their needs • Impact of negative experiences with mental health supports during cancer care • Disappointing approach from cancer care staff when treating patients with SMHD	Facilitators • Cancer decreases the stigma of having a SMHD • Patients with SMHD being able to communicate openly and advocate their needs • Cancer care staff affording understanding and shared decision making with patients
Organizational	Barriers • Biomedical model dominant in cancer care • Difficulties transitioning out of cancer services • Fragmented care delivery between mental and physical health care services	Facilitators • Integrated models of mental health and cancer care • Continued opportunities for engagement with mental health supports • Integrative mental health into cancer care delivery

> I just couldn't take all the pain and constant illness…when I went into hospital…I happened to blubber out to one of the nurses that I had tried to take my life. (P2)

Staying in survival mode as a way of coping

Following cancer diagnosis and the initiation of cancer treatment, some participants described going into "survival mode" as a way of coping and some participants described staying in "survival mode" and shutting down their emotions during their cancer treatment because there was no mental health supports available where participants could feel safe to release their feelings of distress.

> I emotionally shut down…it was very much focused on the physical and the medical, there was no room for the emotional…I did go into survival mode…because there was nowhere, I could safely bring it all out. (P4)

Theme 2: Intrapersonal facilitators

Improved mental health following cancer diagnosis

Some participants reported a considerable decrease in depressive symptoms while also recognizing an increase in their resilience during cancer treatment. One participant recalled a positive shift in her mental health, having had a negative attitude toward her life circumstances in the past. Another participant described her realization regarding how much mental strength and determination that she had, which helped her to progress through her cancer treatment.

> I never wanted to die, especially when I heard I had cancer, I wanted to fight for my life and I think part of that depression lifting could be that fight in me coming up… (P2)

Theme 3: Interpersonal barriers

Patients with SMHD found it difficult to advocate for their needs

The implications of fragmented care delivery between mental health and cancer care services was apparent where some participants felt that mental health difficulties could be missed by cancer care staff if the information was not available on the patient's clinical file. This communication barrier was even more compounded in situations where patients found it difficult to "speak up for themselves" during their treatment.

> For two and a half years, I have been going to these check-ins with…the oncology team and meekly asking…could we maybe fix the hernias I've been left with, and I'm never given a date. And I know it is my mental health where I just don't have the courage or the belief that I'm worth demanding that they fix this bloody thing. (P5)

Disappointing approach from cancer care staff when treating patients with SMHD

Some participants described their disappointment with cancer care staff. One participant recalled being "petrified" on her first day of chemotherapy and described it as a difficult experience for anyone but coupled with her deteriorating mental health she felt even more vulnerable. Despite showing signs of distress and upset, she reported being ignored by cancer care staff. Other participants also described being ignored by cancer care staff and they felt too uncomfortable to ask questions about their care plan during their appointments.

> I have absolutely no qualms in saying that while my oncologist is regarded as a brilliant oncologist; his attitude towards patients was…terrible. In consultations he doesn't…talk to the patient, he talks to the nurse about the patient as if the patient wasn't in the room and I found that very disconcerting. (P5)

Theme 4: Interpersonal facilitators

Cancer decreases the stigma of having a SMHD

After receiving their cancer diagnoses, some participants reported that family members had a more positive attitude toward them, where previously, the same family members would have demonstrated little tolerance toward their mental health difficulties. One participant described feeling more motivated to engage with her cancer treatment because of the positive feedback she was receiving from people in her immediate social support network.

> My relationship with my mother-in-law…when it was discovered I had mental health difficulties, sure I was absolutely broken…It wasn't until she saw me fight cancer that she saw me in a completely different light. (P6)

Patients with SMHD being able to communicate openly and advocate their needs

All the participants identified the importance of feeling comfortable to speak openly about their mental health difficulties during their appointments with cancer care staff. One participant described feeling more confident to speak about her mental health difficulties with medical staff following her cancer diagnosis. She also noted the importance of staff attitudes where openness and a lack of mental health stigma is essential to facilitate an open dialogue about mental health. Participants also found that being able to discuss their mental health difficulties openly with cancer care staff facilitated better treatment engagement as they were encouraged to alert the medical staff if they were struggling. Some

participants also felt that having a higher level of education and being articulate were instrumental to advocating their needs during their cancer treatment.

> High functioning people with a mental health issue…who would be able to say, 'What do you mean by that?', and 'What are the implications of doing it that way?', 'Are there any alternatives?', but not everybody would be able to do that. (P4)

Theme 5: Organizational barriers

Fragmented care delivery between mental and physical health services

Most participants reported that their oncology clinicians did not ask about their mental health history. Even when participants disclosed that they were taking psychotropic medication, cancer care staff rarely sought further information. For most participants, the care they received from mental health and cancer care services was delivered in separate health systems and this proved to be particularly difficult for patients when they were being discharged from services.

> The psychiatric services would be aware that I was finishing my chemo…but the oncology services wouldn't be aware that I was discharged from the psychiatric services…it's like my body was being treated for two completely separate things from two completely separate departments. (P7)

Biomedical model dominant in cancer care

While most participants were satisfied with the standard and efficiency of their cancer care, it was apparent that mental health support was lacking both during cancer treatment and at the follow-up care stage. Some participants felt that their mental health needs were not addressed, and the focus was solely on their physical symptoms. Furthermore, most participants highlighted inadequate staffing and services to support access to mental health support in oncology.

> The oncology nurse co-ordinator…she's an absolute miracle worker but at the same time, she's very dismissive of mental health. I think she's over worked so it's hard for her to take the time to…coddle in the patient who has mental health difficulties. (Participant 5)

Theme 6: Organizational facilitators

Integrated models of mental health and cancer care

Most participants stressed the importance of cancer and mental health services working together as participants reported that the support they received was insufficient at times, and links between services would address

gaps in health care delivery. All the participants reported that cancer services should query the presence of mental health difficulties in a screening questionnaire at the initial appointment.

> I think it should be a question during your first consultation…A standard question, 'Have you ever had any difficulty with a mental health issue? (P2)

Integrative mental health into cancer care delivery

Integrating psychosocial support across the cancer continuum particularly at diagnosis and the completion of acute treatment was identified as a major facilitator among most participants. One participant reported the benefits of having access to mental health support during her treatment, particularly as her cancer care was taking a toll on her marital relationship; she also stressed the importance of accessing mental health support during the follow-up and discharge stage as the transition can be difficult for patients, particularly regarding fear of cancer recurrence.

> Maybe the option of having a discharge chat with your psychologist…because I met a survivor who once said to me, 'Life after cancer can be just as difficult sometimes' …you have got to learn not to panic at every pimple, bump, scrape because you can be plagued with thoughts, 'Is it back? is it back? (P6)

Participants who had access to psycho-oncology support emphasized the importance of helping patients with a range of issues from logistical supports to being an invaluable link between participants, their family members and healthcare professionals from mental health and cancer care services. Another participant noted that every cancer service should have a patient liaison worker to assist patients as they try to navigate fragmented healthcare systems.

Continued opportunities for engagement with mental health supports

All participants had many years of experiencing SMHD and shared that they would value continued opportunities to engage with their mental health teams. Despite the lack of emotional support during their cancer care, most participants reported the difficulty of transitioning out of cancer services and found going from having numerous appointments with the team to (on some occasions) an "abrupt withdrawal of support" from cancer services, had an adverse impact on their mental health.

> One minute there was all this activity and the next minute I was left on my own…I find that very difficult to cope with…certainly a patient who has mental health issues, there is no gradually easing the patient out of the system. (P4)

Discussion

While there are logistical barriers for most patients accessing healthcare services including transport, financial issues, and managing childcare responsibilities[14] as previously mentioned, the focus of the current study was to investigate the potentially modifiable barriers and facilitators that are unique to patients with SMHD when accessing and engaging with cancer care. This qualitative study identified primary intrapersonal, interpersonal and organizational factors that contribute to accessing and engaging with cancer care for individuals with SMHD. Intrapersonal barriers included increased mental health symptoms during cancer care including suicidal ideation. Coupled with additional psychosocial stressors during cancer care (e.g. financial stress, family conflict) some participants found themselves going into "survival mode" during treatment, thus resulting in a delayed emotional response to cancer. This delayed emotional response was further complicated by the lack of mental health supports available at the post cancer treatment phase.

Key intrapersonal and interpersonal facilitators included improved mental health following a cancer diagnosis, utilizing coping strategies learned from mental health supports and increased closeness in family relationships. Additional facilitators included being able to communicate openly and advocate for their needs and cancer care staff understanding patients' needs and facilitating shared decision making with patients in their care. Similar to Sinding and colleagues,[27] some participants in the current study reported a shift in family members' attitudes from a previous intolerance toward participants' SMHD to treating the participants in a more positive manner after their cancer diagnosis. Sinding et al.[27] described the notable improvement in clinical/patient relationships where resources were "mobilised by the cancer diagnosis" and patients with SMHD were generally treated with more respect from healthcare professionals and family members.

Organizational level barriers included the fragmented delivery of cancer and mental health care for individuals with SMHD. Due to a lack of integrated care, some participants reported the implications of being treated for separate health problems by two different departments; one participant reported being discharged from mental health services during cancer treatment, and subsequently being left on psychotropic medication that was managed with a GP who was not familiar with psychotropic medication management. In a previous study Cole and Padmanabhan[28] advocated the need for a team approach to care for patients with SMHD and cancer, as opposed to healthcare professionals working in silos,[27] or assuming that patient needs would be addressed by clinicians in different disciplines. Miller et al.;[15] during a focus group with mental healthcare

professionals, some clinicians noted that addressing preventative physical health issues (e.g. cancer screening) was uncommon and they often assumed that prevention would be addressed by the patients' primary care physician.

Similar to previous studies a person-based approach to care was reported as a key facilitator to improving access to and engagement with cancer care for individuals with a preexisting SMHD.[8,10] A patient navigator was considered to be an essential role to facilitate links between patients and cancer care services, particularly those who struggled to advocate for their needs during their cancer treatment. Similar to the suggestion from Sinding et al.,[27] participants in the current study felt that the person in the patient navigator role should be part of the multidisciplinary team where their main duties are to coordinate care and facilitate communication and access between patients and healthcare services and supports.

Strengths and limitations

The SEM as a theoretical framework provided a comprehensive view of the barriers and facilitators to accessing cancer care for individuals with a preexisting SMHD. Both inductive and deductive methods were adopted to capture the key themes from the patient interviews. This is the first qualitative study to explore patient perspectives regarding barriers and facilitators to accessing and engaging with cancer care for individuals with SMHD in Ireland. The specific geographical location of the sample based across mental health and cancer care services in Ireland, may result in some findings that are unique to the Irish healthcare service. However, the main modifiable factors relating to fragmented care delivery, a need for integrated mental health into cancer care delivery and the development of a patient navigator role are in line with international findings documented in previous research.[8,9,27]

While efforts were made to target more participants for the current study, the implications of COVID-19 impacted our ability to access participants. The specific patient subgroup are a particularly vulnerable group who have difficulties engaging with treatment for their mental and physical healthcare needs,[28] thus it is not surprising that engaging this particular group in research activities has been difficult. The implications of COVID-19 as an additional barrier to accessing healthcare services cannot be overlooked. For three participants the implications of COVID-19 resulted in difficulties accessing mental health support in the community, one participant indicated a preference for face-to-face support as opposed to telephone support from psychiatry. The healthcare restrictions during COVID-19 resulted in the absence of family support for some participants during their cancer treatment, which had negative

consequences on their mental health. COVID-19 did not impact access to cancer care for any of the participants in the current study.

While the current study explored experiences of cancer care among individuals with SMHD, psychiatric inpatients were not included as recommended by clinicians at the recruiting hospitals to avoid the risk of any perceived coercion. As previously noted, adhering to standards of research governance when conducting community based research can be challenging thus placing restrictive limitations on researchers,[29] thus, while potential participants need to be protected from insensitive and intrusive research practices, the absence of their experiences will only result in compounding further marginalization for this specific patient group in addition to a lack of evidence based approaches and further inequalities in their healthcare provision.[30]

Some patients with SMHD may be vulnerable to delays in screening and treatment for cancer, as previously noted based on retrospective chart reviews and interviews with psychiatrists,[31] where a delay in cancer diagnosis was due to communication and behavior disorders, inadequate screening, and patient refusal of additional tests often refused by patients. Participants in the current study were at a higher level of functioning despite having SMHD, thus as participants themselves pointed out, individuals with more severe symptoms or cognitive impairments resulting from SMHD, may be less likely to participate in clinical trials and struggle to advocate their needs and overcome barriers to accessing cancer care. The majority of this small sample had a depression diagnosis and only one participant had schizophrenia. While major depressive disorder is part of the serious mental illness diagnosis, people with schizophrenia and bipolar disorder experience discrimination in the health care system which leads to poorer cancer care;[32] further research which is focused on experiences of patients with schizophrenia and bipolar disorder accessing cancer care is required.

Clinical implications

Consistent with previous research[8,15,27,28] integrated models of care delivery from mental health and cancer care services have potential to address inequalities in cancer care and the associated outcomes for individuals with SMHD while also closing the significant mortality gap. Further focus groups with healthcare professionals from mental health and oncology services would provide greater insight in relation to addressing SMHD in collaboration with psychiatry and tailoring specific training needs to address mental health stigma.

Moments of increased need may include periods of high emotional distress during cancer treatment (particularly diagnosis/recurrences/scans)

and to ease the transition out of cancer care services. A designated patient navigator may be one solution that can support patients with SMHD to navigate a fragmented healthcare system and have potential to prevent patients from missing needed cancer treatment.

Conclusion

Cancer care for people with SMHD is currently insufficient, with a significant mortality gap compared to the general population.[33,34] Inequities in cancer care delivery will continue to rise with the increasing cancer rates proposed in the future,[35] thus, addressing the needs for this specific population should be a priority. The findings outlined in this paper strengthen the evidence for the importance of facilitating integrated models of mental health and cancer care delivery for patients with SMHD. This preventable cancer disparity for people with SMHD can be addressed by incorporating early mental health involvement, and integrated mental health and cancer care team-based approaches to care.

Author contributions

All authors contributed to this work and authorship of this manuscript. D.L. planned, conducted the search, collected the data, analyzed the results, wrote and reviewed the manuscript; KI provided writing and review support, GM facilitated data collection and provided writing supports, P.D. acted as a second coder and provided writing and review support.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

The author(s) reported there is no funding associated with the work featured in this article.

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Appendix A

Table A1. Consolidated Criteria for Reporting Qualitative Research (COREQ).[17]

COREQ item	Guide questions/description	
Domain 1: Research team and reflexivity		
Interviewer/facilitator identified	Which author/s conducted the interview or focus group?	DL
Researcher credentials	What were the researcher's credentials? E.g., PhD, MD	PhD
Occupation of researcher	What was their occupation at the time of the study?	Psychologist in Clinical Training
Gender of researcher	Was the researcher male or female?	Female
Experience and training	What experience or training did the researcher have?	Previous training in qualitative research and 14 years conducting both research and clinical interviews across arrange of populations (e.g., young stroke survivors, young people and health care professionals regarding mental health, addiction, self-harm and suicide
Prior/existing relationships with participants	Was a relationship established prior to study commencement?	DL was not known to any of the study participants prior to study participation, where participants would have contacted DL to express and interest in the study.
Participant knowledge of interviewer	What did the participants know about the researcher? e.g., personal goals, reasons for doing the research	Participants were aware from the clinician / nurse assisting with recruitment and the study information leaflet that the interviewer was a Psychologist in Clinical training affiliated with the HSE and UCD and they were provided with the interviewer's contact information if they wished to find out more about the study
Interviewer characteristics, for example bias, assumptions, interest in topic	What characteristics were reported about the interviewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	The interviewer's background as a Psychologist in Clinical Training, and also having recently completed a systematic review based on the topic of people with SMHD accessing cancer care, it would not be possible to omit the fact DL had prior assumptions based on previous research findings and also she was being supervised and mentored by PD and KI, both clinicians and researchers with numerous years of experience in the area of SMHD and cancer care.
Domain 2: Study Design		
Theoretical framework		
Methodology and theory	What methodological orientation was stated to underpin the study? e.g., grounded theory, discourse analysis, ethnography, phenomenology, content analysis	Inductive and deductive thematic analysis, using the SEM as the theoretical framework
Participant selection		
Sampling strategy	How were participants selected? e.g., purposive, convenience, consecutive, snowball	Purposive
Method of approach/ invitation	How were participants approached? e.g., face-to-face, telephone, mail, email	Face-to-face by nursing staff for hospital recruitment and social media channels linked with relevant mental health and cancer organisations (e.g., twitter, LinkedIn, and Facebook)

Sample size	How many participants were in the study?	7
Non-participation	How many people refused to participate or dropped out? Reasons?	1 participant dropped out and 3 participants did not meet the inclusion criteria
Setting		
Setting of data collection	Where was the data collected? e.g., home, clinic, workplace	Interviews were conducted over the phone
Presence of non-participants	Was anyone else present besides the participants and researchers?	No
Description of sample, for example, demographics	Was anyone else present besides the participants and researchers?	Demographic details including marital status, employment status, etc. included in the results section.
Data collection		
Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?	Yes (Appendix A)
Repeat interviews	Were repeat interviews carried out? If yes, how many?	No
Audio/visual recording	Did the research use audio or visual recording to collect the data?	Audio recording
Field notes	Were field notes made during and/or after the interview or focus group?	Yes, demographic information was recorded at the start of the interview.
Duration	What was the duration of the interviews or focus group?	Interviews ranged from 33 minutes to 2 hours 49 minutes
Data saturation	Was data saturation discussed?	Yes
Transcripts returned	Were transcripts returned to participants for comment and/or correction?	Yes, 5/7 participants requested a copy of their interview transcript when it was offered prior to participation.
Domain 3: Analysis and findings		
No of data coders	How many data coders coded the data?	2
Description of coding tree	Did authors provide a description of the coding tree?	No
Derivation of themes - in advance or derived	Were themes identified in advance or derived from the data?	Both
Software	What software, if applicable, was used to manage the data?	Nvivo 12
Participant checking	Did participants provide feedback on the findings?	No
Quotations presented	Were participant quotations presented to illustrate the themes / findings? Was each quotation identified? e.g. participant number	Yes
Data and findings consistent	Was there consistency between the data presented and the findings?	Yes
Clarity of major themes	Were major themes clearly presented in the findings?	Yes
Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	Yes

Appendix B. Interview schedule

1. **Background**
   Can you please begin by telling me what type of mental illness you have and how long you have been affected by this illness for?
   Okay we will now move onto your experiences with cancer care:
2. **Cancer diagnosis**
   Before being diagnosed with cancer, how long were you experiencing distressing symptoms?
   Can you tell us a little bit about your diagnosis?
   Can you identify any barriers that prevented you from seeking initial help for these symptoms?
   Can you identify any facilitators that encouraged you to seek initial help for these symptoms?
   Did this healthcare professional have knowledge of your [insert relevant mental illness]?
   Were you able to attend all meetings and tests that were scheduled for you?
   Did you feel like you were being supported through the process at this time by healthcare professionals?
   Did you seek, refuse or deny any psychiatric care at this stage?
   Did you notice any changes to your symptoms of [insert relevant mental illness] at this time?
3. **Initial oncology consultation**
   Following your diagnosis, how long was it before your initial meeting with your oncologist was scheduled?
   Did you attend this consultation?
   Can you tell me your experience of this consultation?
   Did you find it informative?
   Was it supportive?
   Did you attend the consultation alone or with a family member/friend/partner?
   Did you talk about your [insert relevant mental illness] with the consultant present?
   Did anyone present raise any concerns over how your mental illness might affect your cancer treatment?
   At this post-diagnosis stage, did your symptoms of [insert relevant mental illness] change?
   Did you seek, refuse or deny psychiatric care at this stage?
4. **Cancer treatment**
   Can you describe your experience of cancer care during the treatment stage?
   Did you experience any delays or interruptions in your cancer care? What might lead to such delays or interruptions?
   In your experience, what helps cancer care go well? (to avoid delays/interruptions).
   Did you feel your [insert relevant mental illness] affected the care you received at this stage?
   Did you miss any scheduled appointments due to your [insert relevant mental illness]?
   If yes: were these meetings rescheduled promptly?
   Did you find that healthcare professionals were understanding of your [insert relevant mental illness]?
   Did you seek, refuse or deny psychiatric care at this stage?
   Do you think cancer patients who also have [mental illness] and other mental illnesses require more care than other cancer patients?

5. Process of Follow-Up

Following your cancer treatment, what was your experience of the process of follow-up? At this stage, did notice any changes to your symptoms of [insert relevant mental illness]?

Did you seek, refuse or deny psychiatric care at this stage?

Can you identify any barriers that might have prevented you from attending follow-up appointments?

Can you identify facilitators that encouraged you to follow-up with your oncologist?

6. Quality of cancer care

Okay so I'd just like to take this moment to thank you so far for sharing your experiences. Before we close, I would like to find out your personal opinions regarding the quality of cancer care for patients with significant mental health experiences. Do you feel patients with such difficulties receive equal quality of care as other cancer patients?

Can you identify any barriers to such care?

Can you identify any facilitators to such care?

Please share any ideas of how you think that we could improve the care of patients with SMHD.

Did you link in with Psycho-Oncology services? At what stage? Tell me a little more about your decision to link in with them? What did you think you would find helpful? Looking back what would have helped?

In closing, is there anything else that you'd like to add? Anything that we didn't ask?

Thank you again for your time and participation. We are now finishing recording.

Personalized Medicine

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ipme20

A Real-World Analysis of Tyrosine Receptor Kinase Inhibitor-Related Toxicities in Cancer Treatment

Wenjie Li, Keshan Wen, Weijie Zhu & Shangfei Luo

To cite this article: Wenjie Li, Keshan Wen, Weijie Zhu & Shangfei Luo (2023) A Real-World Analysis of Tyrosine Receptor Kinase Inhibitor-Related Toxicities in Cancer Treatment, Personalized Medicine, 20:6, 485-491, DOI: 10.2217/pme-2023-0072

To link to this article: https://doi.org/10.2217/pme-2023-0072

Short Communication

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Personalized Medicine

A real-world analysis of tyrosine receptor kinase inhibitor-related toxicities in cancer treatment

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Background: This study analyzed real-world data from 2004 to 2023 to evaluate the toxicity profile of tyrosine receptor kinase (TRK) inhibitor therapy. **Method:** A retrospective analysis of US FDA Adverse Event Reporting System data was conducted to identify adverse events in patients receiving TRK inhibitor therapy. **Result:** Entrectinib demonstrated toxicities primarily in the cardiovascular and nervous systems, followed by the renal and urinary system. Common adverse effects included dizziness, renal impairment, constipation, heart failure and taste disorders. Larotrectinib induced adverse events mainly in the hepatobiliary and nervous systems, with peripheral neuropathy, myalgia, renal impairment and increased alanine aminotransferase commonly reported. **Conclusion:** Careful monitoring and supportive care strategies are essential for managing adverse events associated with TRK inhibitor therapy.

First draft submitted: 15 June 2023; Accepted for publication: 22 September 2023; Published online: 1 November 2023

Keywords: cancer • FAERS • safety • toxicity profile • TRK inhibitor

Targeted therapy has revolutionized cancer treatment by providing effective and less toxic options compared with conventional chemotherapy. One promising therapeutic target is *NTRK* gene fusion. *NTRK* gene fusions play a significant role as a driver of carcinogenesis in various cancers by causing rearrangements of the tyrosine receptor kinase (TRK), leading to its hyperactivation, which stimulates cell proliferation and differentiation [1,2]. By inhibiting TRK activity, TRK inhibitors (TRKis) can effectively target cancer cells that rely on TRK signaling for growth and survival, thus emerging as an auspicious target for therapeutic intervention. In 2018, the US FDA approved first-generation TRKis, such as entrectinib and larotrectinib, for use in patients with *NTRK* fusions in a broad range of cancers. Moreover, previous clinical trials have observed response rates of over 75% and robust disease control [3,4], making them a promising therapeutic arsenal.

However, current guidelines for the use of TRKis are not specific to cases that harbor *NTRK* fusions. Furthermore, like any other cancer therapy, TRKis have potential side effects and toxicities. Several preclinical or prospective studies with strict inclusion criteria and small sample sizes have shown certain adverse events (AE) of TRKis [5,6]. However, the toxicity profile of these inhibitors in a real-world setting remains unclear. A comprehensive understanding of the toxicity profile of TRKis is crucial in ensuring safe clinical use in the real world. Thus, this study aimed to investigate the potential toxicities associated with TRKis in the FDA Adverse Event Reporting System (FAERS). The authors also highlight the long-term safety concerns associated with TRKis and the need for further research to address these concerns. Adequate patient selection, monitoring and supportive care measures can help mitigate these toxicities and ensure the safe use of TRKis in cancer treatment.

Future Medicine

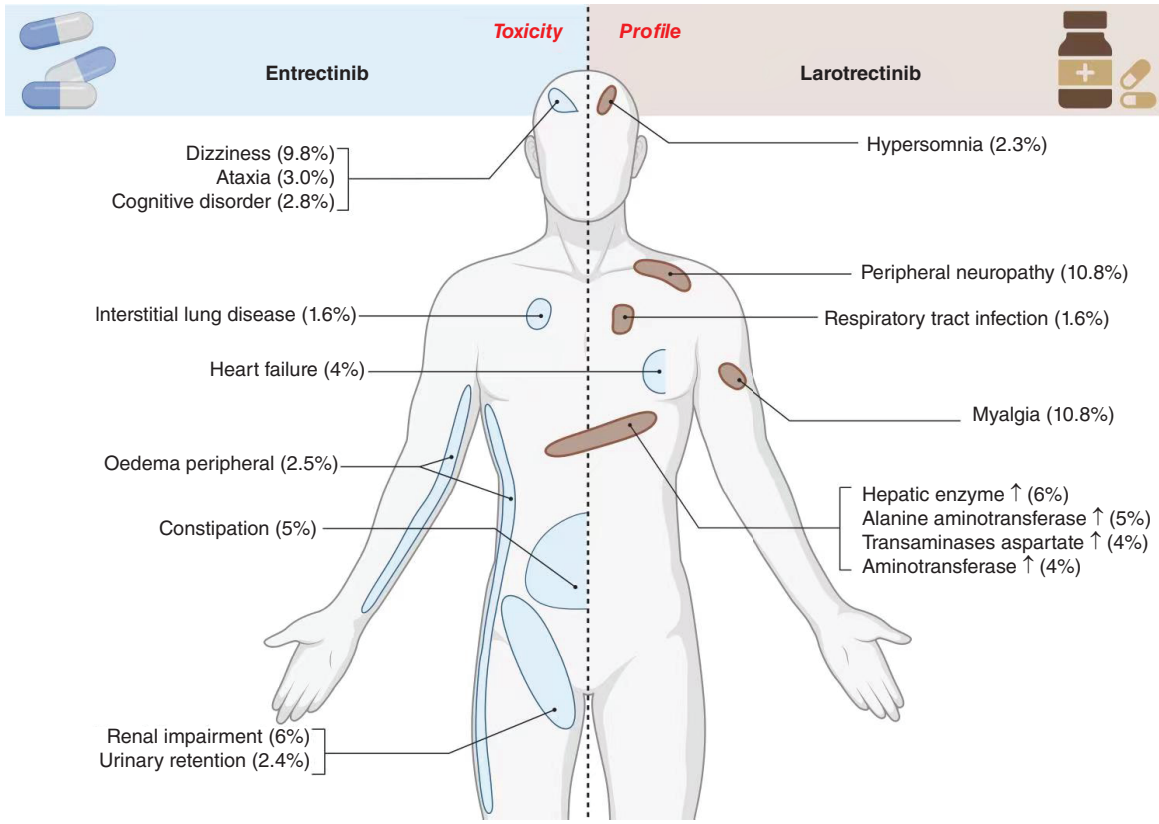

Figure 1. Toxicity profile of tyrosine receptor kinase inhibitors (entrectinib and larotrectinib). The upward arrow symbolizes an elevation in the levels of hepatic enzymes, specifically alanine aminotransferase and aspartate aminotransferase.

Methods

FAERS is a project that has been used to estimate the safety of approved products in the real world. The authors conducted a retrospective analysis of FAERS data obtained from 2004 to 2023 (www.fda.gov/). Data related to cancer patients who received the first-generation TRKis (entrectinib and larotrectinib) were extracted using OpenVigil 2.1 (https://openvigil.sourceforge.net/) [7]. AEs were coded using the Medical Dictionary for Regulatory Activities terminology, preferred term and system organ class. The authors analyzed the overall incidence and prevalence of AEs, as well as the severity and seriousness. To ensure the validity and reliability of the results, reporting odds ratio (ROR) [8] and the Bayesian Confidence Propagation Neural Network (BCPNN) [9] were employed to estimate significant AEs. Calculations of ROR and BCPNN were well described in previous work. Lower 95% CIs of ROR >1 and BCPNN >0 were defined as statistical significance, respectively. High values of ROR and BCPNN indicated more robust associations between side effects and TRKi treatment. Data manipulation was performed using R software (version 4.2.0).

Results

In this study, the authors identified a total of 1088 oncologic cases who received treatment with TRKis. Of these cases, 638 were administered entrectinib and 450 were given larotrectinib. Among the identified cases, 45.85% were male, and the majority of patients ($n_{entrectinib}$ = 306; $n_{larotrectinib}$ = 246) were from the USA. The findings suggested that neither entrectinib nor larotrectinib contributed to any serious AEs such as death or hospitalization (Supplementary Table 1).

Entrectinib was found to exhibit toxicities primarily in the cardiovascular system (n = 210; 33.23%) based on real-world data, followed by the nervous system (n = 149; 23.58%), renal and urinary system (n = 133; 17.88%), gastrointestinal system (n = 46; 7.23%) and endocrine system (n = 30; 4.74%), as presented in Figures 1 & 2. Among the most commonly reported AEs observed with entrectinib administration were dizziness (n = 60; 9.8%;

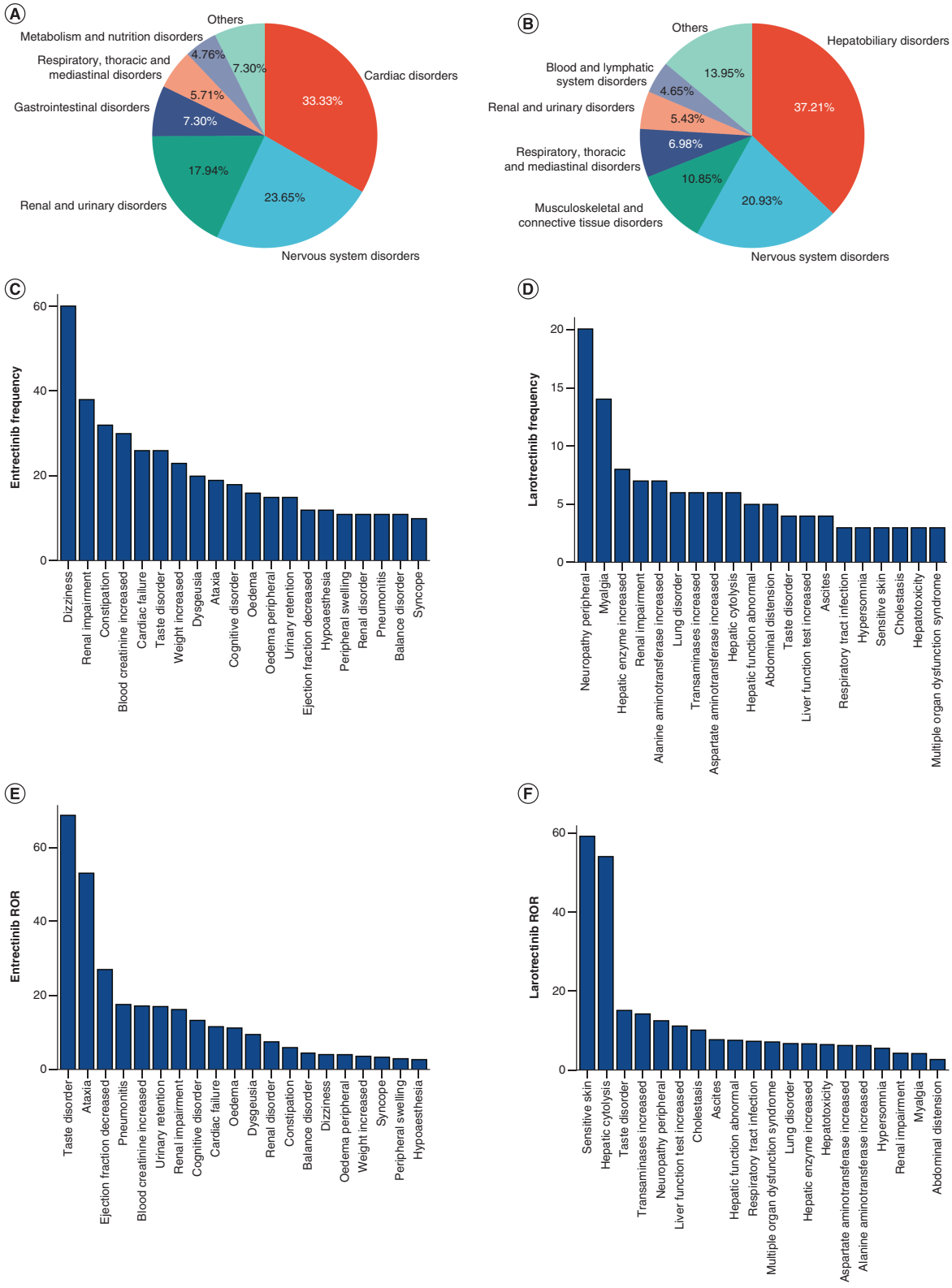

Figure 2. Proportion of adverse events. Adverse effects in different systems of **(A)** entrectinib and **(B)** larotrectinib. The top 20 adverse effects according to frequency in **(C)** entrectinib and **(D)** larotrectinib and reporting odds ratio in **(E)** entrectinib and **(F)** larotrectinib.
ROR: Reporting odds ratio.

ROR: 4.31; 95% CI: 3.31–5.62), renal impairment (n = 38; 6%; ROR: 16.43; 95% CI: 11.84–22.81), constipation (n = 32; 5%; ROR: 16.43; 95% CI: 11.84–22.81), heart failure (n = 26; 4%; ROR: 11.81; 95% CI: 7.98–17.49), taste disorder (n = 26; 4%; ROR: 6.20; 95% CI: 4.34–8.34), weight gain (n = 23; 3.6%; ROR: 3.86; 95% CI: 2.55–5.85), dysgeusia (n = 20; 3.1%; ROR: 9.71; 95% CI: 6.22–15.17), ataxia (n = 19; 3.0%; ROR: 53.10; 95% CI: 33.62–18.88) and cognitive impairment (n = 18; 2.8%; ROR: 13.51; 95% CI: 8.45–21.59). These findings highlight the importance of further investigations into the safety and tolerability of entrectinib, particularly in diverse patient populations (Supplementary Table 2).

Larotrectinib-induced AEs were predominantly observed in the hepatobiliary system (n = 68; 37.21%), followed by the nervous system (n = 27; 20.93%), musculoskeletal and connective tissue system (n = 14; 10.85%), respiratory system (n = 9; 6.97%) and renal and urinary system (n = 7; 5.42%; Figures 1 & 2). Further, the top ten side effects most commonly reported with larotrectinib were peripheral neuropathy (n = 20; 15%; ROR: 13.51; 95% CI: 8.45–21.59), myalgia (n = 14; 10.85%; ROR: 4.28; 95% CI: 2.51–7.28), renal impairment (n = 7; 5.4%; ROR: 4.35; 95% CI: 2.06–9.19), alanine aminotransferase increase (n = 7; 5.43%; ROR: 6.29; 95% CI: 13.27–2.98), lung disorder (n = 6; 4.65%; ROR: 6.79; 95% CI: 15.2–3.03), transaminases increase (n = 6; 4.65%; ROR: 14.25; 95% CI: 31.91–6.37), aspartate aminotransferase increase (n = 6; 4.65%; ROR: 6.32; 95% CI: 14.14–2.82), hepatic cytolysis (n = 6; 4.65%; ROR: 53.92; 95% CI: 120.78–24.07) and hepatic function abnormality (n = 5; 3.88%; ROR: 7.62; 95% CI: 18.39–3.15; Supplementary Table 2). These findings warrant further exploration into the risk–benefit assessment of larotrectinib administration and its potential toxicity in diverse patient groups.

Subsequently, a comparative analysis was conducted on the top 20 AEs using both the FAERS and United States Prescribing Information (USPI) databases (Supplementary Table 3) for reference. Notably, common AEs observed in both entrectinib groups encompassed myalgia, neurotoxicity, elevated levels of alanine aminotransferase and aspartate aminotransferase and hepatotoxicity. Conversely, contrary to the findings in the FAERS database, the prominent AEs highlighted in the USPI data included anemia, fatigue, hypoalbuminemia, nausea, vomiting, cough and constipation. In regard to larotrectinib, commonly reported AEs were constipation, increased creatinine, weight gain, dysgeusia, dysesthesia and edema. However, anemia, fatigue, lymphopenia, dizziness, diarrhea, hypernatremia, nausea and dyspnea were more prevalent in the USPI records. It is important to note that the data sourced from the USPI primarily relied on information obtained from clinical trials, wherein the incidence of AEs tended to be relatively higher compared with real-world settings (Supplementary Table 3).

Discussion

TRKis, including entrectinib and larotrectinib, have demonstrated efficacy in patients with TRK fusion-positive cancers. However, the present study of AEs associated with these agents revealed distinct toxicity patterns. For entrectinib, the most common AEs were related to cardiovascular (33.23%), nervous (23.58%) and renal and urinary system (17.88%) toxicities. In contrast, AEs associated with larotrectinib were primarily observed in the hepatobiliary system (37.21%), nervous system (20.93%) and musculoskeletal and connective tissue system (10.85%). These findings underscored the need for vigilant monitoring of patients receiving TRKis, particularly those with pre-existing above comorbidities.

This analysis highlights several noteworthy toxicity profiles of TRKis. First, cardiac toxicity is a potential concern, particularly with the use of entrectinib. Cardiotoxicity in the real-world setting was mainly represented by heart failure, peripheral edema, syncope, decreased ejection fraction, cardiomyopathy, arrhythmia and left ventricular dysfunction. Prior research indicated that TRK inhibition leads to cardiac dysfunction through dysregulation of phosphorylation and the endothelin system [10]. Consistent with phase I–II clinical studies [6], the current findings also suggest that TRK inhibition increases the risk of a range of cardiovascular AEs. However, the rate of cardiotoxicity in phase I–II clinical trials was less than 3%, while this study revealed a much higher incidence of 33.23% in the real-world setting. This discrepancy may be partly due to the relatively small sample size, lower or specific doses of entrectinib and fewer comorbidities observed in clinical trials. Second, neurotoxicity is another potential concern with TRK inhibitor therapy, and this study's findings aligned with prior studies [5,6]. The authors observed that dysgeusia, dizziness, paresthesia and ataxia were the most common side effects associated with entrectinib, while peripheral neuropathy and hypersomnia were more frequently observed in patients receiving larotrectinib. Third, renal toxicity is another relevant AE associated with entrectinib therapy. Despite approximately 15% of patients experiencing increased blood creatinine levels in phase I–II clinical studies [6], only 5% of cases were identified in this real-world analysis. Fourth, the authors noted that hepatotoxicity was the most frequently observed AE associated with larotrectinib, consistent with both the real-world analysis and clinical trials. Alanine

aminotransferase or aspartate aminotransferase increased in the majority of larotrectinib-treated cases. Despite the relatively low incidence, gastrointestinal and respiratory toxicity have also been reported with TRKis. Fifth, the authors conducted a comparative analysis of the top 20 AEs using data from the FAERS and USPI databases. The findings revealed notable disparities between these databases regarding the reported AEs for entrectinib and larotrectinib. Within the entrectinib group, the commonly reported AEs in both databases included myalgia, neurotoxicity, increased alanine aminotransferase and aspartate aminotransferase levels and hepatotoxicity. However, the USPI database listed additional AEs, such as anemia, fatigue, hypoalbuminemia, nausea, vomiting, cough and constipation, which were not documented in the FAERS database. For larotrectinib, common AEs reported across both databases encompassed constipation, increased creatinine levels, weight gain, dysgeusia, dysesthesia and edema. Conversely, anemia, fatigue, lymphopenia, dizziness, diarrhea, hypernatremia, nausea and dyspnea were more commonly reported in the USPI database. It is noteworthy that the data in the USPI database primarily originate from clinical trials, where the incidence of AEs may be relatively higher compared with real-world settings. This study's findings underscore the importance of monitoring and managing the toxicity profiles associated with TRKis and will aid clinicians and researchers in devising an optimal dose and administration strategy for TRKis.

Two factors may account for the divergence in AEs between the larotrectinib and entrectinib cohorts. One underlying mechanism stems from the disparate modes of action of both agents. Entrectinib, functioning as a multikinase inhibitor, possesses the capacity to impede a broader spectrum of kinases (e.g., ROS1 and ALK) than TRK receptors exclusively (e.g., TrkA, TrkB, TrkC) [11]. Consequently, this broader kinase blockade may engender a wider array of AEs, including potential off-target toxicities. Prevalent AEs accompanying entrectinib treatment encompass dizziness, renal impairment, constipation, heart failure, taste disturbance, weight gain, dysgeusia, ataxia and cognitive impairment. Contrariwise, the selective inhibition of TRK receptors by larotrectinib can generate a more concentrated AE profile. Primary AEs associated with larotrectinib therapy predominantly embrace peripheral neuropathy, myalgia, renal impairment, lung disorders, heightened alanine aminotransferase, augmented transaminases, increased aspartate aminotransferase, hepatic cytolysis and abnormal hepatic function. Importantly, these AEs align with the inhibition pattern of TRK signaling and are generally deemed manageable and reversible. It should be noted, however, that the larotrectinib cohort comprised a significantly greater ratio of pediatric patients than the entrectinib cohort. Pediatric patients may exhibit disparities in drug metabolism, response and tolerability in comparison with adults. Unique physiological attributes found in pediatric patients, such as immature organ systems, developmental changes and variations in body size, can influence the processing of medications and impact safety profiles. Hence, any discernible dissimilarities in AEs between the two medications could be influenced by these patient characteristics. Further scrutiny and investigation are essential to ascertain whether the higher proportion of pediatric patients in the larotrectinib group markedly influences AE profiles or if other factors also influence the outcomes.

NTRK fusion genes are expressed in approximately 0.3–1.6% of all solid tumors, but the expression rate can vary greatly among different types of cancer [12]. Salivary gland secretory carcinomas, in particular, have a high rate of *NTRK* fusion gene expression, mainly involving the ETV6-*NTRK*3 fusion gene. It is therefore crucial to identify secretory carcinomas and test for ETV6-*NTRK*3 gene rearrangements to guide patient care. For instance, there was a case of a 44-year-old patient with recurrent parotid carcinoma positive for the ETV6-*NTRK*3 gene fusion who achieved a complete response to entrectinib treatment, although he experienced additional side effects such as dysgeusia, fatigue and dizziness, which were alleviated by reducing the entrectinib dose [13]. Recent studies have also reported positive responses to TRKis in other cancer types with relatively low frequencies of *NTRK* fusions. For example, Recine *et al.* [14] reported a case of a young adult with a metastatic spindle cell neoplasm and high tumor burden harboring a rare *NTRK* fusion gene partner (TPM4-*NTRK*1), who achieved a rapid response to larotrectinib without experiencing side effects, thus maintaining a good quality of life. Nevertheless, notwithstanding the commendable efficacy of TRKis, it is imperative to acknowledge the challenges associated with *NTRK* detection in specific malignancies owing to the intricacies of signal patterns, such as colorectal cancer [15] and liver carcinomas [16]. Due to the absence of immunoreactivity for the ETV6-*NTRK*3 fusion gene, there is a possibility of overlooking its presence during pan-TRK immunohistochemistry screening [15]. Immunohistochemistry targeting TRK expression also may yield a substantial number of false-positive results, necessitating validation on comprehensive tissue sections and confirmation through molecular genetic analyses, such as RNA sequencing [16]. Importantly, both larotrectinib and entrectinib, classified as first-generation pan-TRKis, have demonstrated promising clinical efficacy in various clinical trials. However, the duration of response has been limited by mutations that occur in the protein structure, leading to resistance to these inhibitors. Notable

mutations include solvent-front mutations, xDFG motif mutations and gatekeeper mutations. These mutations induce changes in amino acids that hinder the binding of inhibitors to the ATP binding site. To overcome these challenges, second-generation TRKis, such as selitrectinib and repotrectinib, have been developed [17]. These inhibitors can effectively address solvent-front mutations [11,17]. Larotrectinib, entrectinib and selitrectinib belong to type I TRKis, demonstrating high selectivity for pan-TRK enzymes [11]. Repotrectinib, on the other hand, is a multikinase inhibitor capable of inhibiting TRK, ROS1 and ALK enzymes. However, selitrectinib and repotrectinib are unable to overcome xDFG mutations due to their less selective patterns in type I TRKis [12]. To address this limitation, type II inhibitors have been developed as more selective compounds that can bind to the mutant xDFG and overcome acquired resistance [18]. Additionally, type III TRKis have been designed to target an allosteric pocket located distantly from the ATP binding site [11,19].

By and large, TRKi therapy offers a promising option for cancer treatment in a subset of patients with *NTRK* gene fusions. However, the toxicity profile of these drugs warrants careful consideration, particularly with respect to cardiotoxicity, neurotoxicity and hepatotoxicity. Future research is necessary to better understand the mechanisms of these toxicities and to develop effective management strategies that can minimize the risks of TRKi therapy while maximizing its therapeutic benefits. An important limitation of the present study is the absence of detailed data on specific *NTRK* gene isotypes and cancer subtypes within the FAERS database. Understanding the variations in AEs based on these factors is essential for a comprehensive analysis. Future studies incorporating more granular data on *NTRK* gene isotypes and cancer subtypes would contribute to a more thorough understanding of the observed differences in AEs.

Conclusion

Entrectinib exhibited toxicities mainly in the cardiovascular and nervous systems, whereas larotrectinib-induced AEs were predominantly observed in the hepatobiliary and nervous systems. Close monitoring and supportive care measures can help manage AEs associated with TRKis, especially for cardiovascular toxicity, nervous toxicity and hepatotoxicity.

Summary points

- The toxicity profile of TRK inhibitor therapy in a real-world setting is not well understood.
- A comprehensive analysis of US FDA Adverse Event Reporting System data from 2004 to 2023 was conducted to extract reports of adverse events in patients receiving TRK inhibitor therapy.
- Real-world data revealed that entrectinib primarily exhibited toxicities in the cardiovascular system, followed by the nervous system and renal and urinary system.
- The most commonly reported adverse events associated with entrectinib administration included dizziness, renal impairment, constipation, heart failure and taste disorder.
- Larotrectinib-induced adverse events were predominantly observed in the hepatobiliary and nervous systems, followed by the musculoskeletal and connective tissue system.
- The most commonly reported side effects associated with larotrectinib were peripheral neuropathy, myalgia, renal impairment and increased alanine aminotransferase.
- Careful monitoring and supportive care measures are essential for managing the adverse events associated with TRK inhibitor therapy.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/pme-2023-0072

Author contributions

W Li and K Wen: conceptualization, methodology, data curation, software and writing – review and editing; W Zhu and S Luo: visualization. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

Acknowledgments

The authors appreciate the work of the FAERS database (www.fda.gov/).

Financial disclosure

The authors have no financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties.

Competing interests disclosure

The authors have no competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties.

Writing disclosure

No writing assistance was utilized in the production of this manuscript.

Data availability statement

The original data are available in the FAERS database (www.fda.gov/).

Ethical conduct of research

No ethics approval and written consent were needed for the secondary analysis of public data.

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Interview

Oncology Central

The more the better? Quadruplets in newly diagnosed multiple myeloma

Carl Ola Landgren is a Professor of Medicine, Chief of the Myeloma Division, and Co-Leader of the Translational and Clinical Oncology (TCO) Program at NCI-designated Sylvester Comprehensive Cancer Center (FL, USA). As a Cancer Center Support Grant member, he participates in research activities as an independent investigator, as a leader of research governance committees, and serves on multi-disciplinary research teams. He is a frequent speaker and faculty member for national and international meetings on myeloma and hematologic malignancies.

Landgren recently presented at the 2024 ASCO Annual Meeting (May 31–June 4, IL, USA) about the potential of quadruplet therapies in newly diagnosed multiple myeloma. In this interview, he provides a breakdown of key takeaways from his talk and discusses challenges and opportunities in this area.

What were the key takeaways from the discussion on quadruplet therapy approaches in multiple myeloma presented at this years ASCO?

By adding a fourth drug to an existing backbone with three drugs, it provides a higher degree of efficacy (more MRD negativity and longer progression free survival (PFS)) than the three drugs alone. This is true for both younger, fit (so-called transplant eligible) and older, frail (so-called transplant ineligible) patients. We are seeing higher and higher rates of deep treatment responses (i.e., MRD negativity) and longer PFS with novel four-drug combinations “quadruplets”, independent of transplant status. It raises the question of whether it is time to retire the more than 40-year old terminology “transplant eligible/ineligible” and instead just use the terminology “newly diagnosed multiple myeloma”.

Interview

What are the challenges of using quadruplet therapies?

Adding more drugs always comes with adverse events. Adding immunotherapy may increase the risk of infection, which is all manageable. Adding the proteasome inhibitor bortezomib to a three-drug combination with an IMiD, a CD38 targeted antibody, and dexamethasone, bortezomib increases the risk of peripheral neuropathy. Bortezomib has a quite high rate of peripheral neuropathy that is clinically relevant (grade 2 or higher), somewhere around 50% of all patients treated with bortezomib have peripheral neuropathy. Alternative strategies, to avoid bortezomib, include the use of newer proteasome inhibitors, such as carfilzomib; or potentially using bispecific monoclonal antibodies, which is currently being investigated in ongoing clinical trials. The field is moving fast forward.

What elements of multiple myeloma make it a good candidate for this and what other cancer types could this approach be used for?

As stated above, by adding a fourth drug to an existing backbone with three drugs – a quadruplet, provides a higher degree of efficacy (more MRD negativity and longer PFS) than the three drugs alone. Also, it raises the question if transplants are truly needed in the modern era. Large randomized studies done in the modern era show that transplants do not prolong overall survival. Perhaps, using more effective four-drug combinations (quadruplets) is the new way going forward, and – overall – transplants will have more of a role in the relapse setting? Importantly, CAR T cell therapy was recently US FDA approved in the setting of a first replace in multiple myeloma. As previously mentioned, the field is moving fast forward.

What are you most looking forward to at ASCO this year?

I look forward to hearing all the presentations on new therapies on multiple myeloma. I also look forward to giving my talk as a discussant, summarizing and discussing the talks on novel quadruplets in the setting of newly diagnosed multiple myeloma. I also look forward to networking with colleagues in the field.

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