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Toxicities associated with immunotherapies for hematologic malignancies

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ABSTRACT

Immunotherapy has generated tremendous hope for patients with cancer that is refractory to standard approaches. Hematologic malignancies have taken the lead in harnessing the most recent advances in cell-based immunotherapies, such as CAR T cells, and some patients have achieved durable remissions. However, these T-cell-engaging therapies are associated with a new set of toxicities which need to be managed by caretakers, oncologists, nurses, and healthcare staff. In this review we provide an overview of the toxicity of some of these revolutionary agents including bispecific T cell engagers, checkpoint inhibitors, chimeric antigen receptor T-cells.

1. Intro

Dr. William Coley is considered by many to be the “Father of Immunotherapy” after he first injected streptococcal bacterial cultures into patients with inoperable cancers in 1891 and reported tumor regression [1]. It would be another 80 years before Donnall Thomas and others were able to harness allogeneic stem cell transplantation to cure acute leukemia. Since the first successful allogeneic stem cell transplantation for acute leukemia in 1969 [2], immunotherapy has continued to provide the promise of effective therapy. Progress has been slow and toxicity was greater than anticipated: even 20 years after Dr. Thomas' first reports, allogeneic stem cell transplantation for some types of leukemia still failed to show an overall survival benefit due to toxicity [3].

The next generation of immunotherapy after transplant came in the form of monoclonal antibodies and have been a tremendous success story in hematologic malignancies since the approval of rituximab in 1997. Nearly 80 therapeutic monoclonal antibodies are FDA approved as of 2018, with a great number being used in cancer [4]. Antibody-drug conjugates followed as a natural next step, with brentuximab, the anti-CD30 antibody linked to antimitotic agent monomethyl auristatin E (MMAE, also known as vedotin), taking the lead in this space. Further efforts to harness the immune system led to the novel bispecific T-cell engager blinatumomab, which received accelerated FDA approval in 2014. Simultaneously, successful treatment came in the form of CD19 targeted chimeric antigen receptors for patients with aggressive chronic lymphocytic leukemia (CLL) [5]. Interest in CAR-T cells and immunotherapy has increased exponentially with now two FDA approved CAR-T cell products in 2017; Kymriah for acute lymphoblastic leukemia (ALL) and Yescarta for large B cell lymphoma. This path has not been without causalities with twenty deaths attributed to CAR-T in trials cells since 2010 [6]. We have now entered a new era of immunotherapy with its own panoply of life threatening toxicities. However, decades of work to characterize the underpinnings of the immune system and improvements in supportive care have given clinicians the tools to better recognize, adapt, and respond to toxicities of these agents in real time.

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1.1. Bispecific T-cell engagers

Bispecific T-cell engagers (BiTEs) are link two single-chain variable fragments derived from monoclonal antibodies that link T cells via their CD3 receptor to tumor surface antigens. Mechanistically, this brings T-cells into direct contact with a given target, and trigger T cell activation. The most successful agent in this class is blinatumomab, a CD19 targeted conjugated in which targets CD19. The response is major histocompatibility complex (MHC) independent and results in a polyclonal T-cell response with $CD4^+$ and $CD8^+$ and mostly effector subsets [7,8]. This is advantageous as an off-the-shelf therapy since it is effective regardless of HLA subtype and does not require specialized processing. Based on dramatic early success, Blinatumomab was granted accelerated approval in Philadelphia chromosome negative relapsed or refractory B-cell precursor ALL followed by full approval in 2017 [9].

Blinatumomab has shown powerful responses in chemorefactory patients [8,10,11]. Robust T-cell activation comes with a cost, however, and the drug comes with a black box warning for both CRS and neurotoxicity [12]. Fortunately, serious side effects are relatively rare. The phase I trial of patients with non-Hodgkin lymphoma found just one of thirty-eight patients experienced grade 3–4 neurotoxicity, though some patients did experience less severe disorientation, confusion, speech disorders, tremor and convulsions which were fully reversible after discontinuation [13]. The most common grade three or higher adverse events were lymphopenia (68%), elevated CRP (34%), and leukopenia (23%), neutropenia (15%). In a population of B-ALL patients with minimal residual disease just one of twenty-one patients experienced grade 3–4 neurotoxicity. The most common side effect was lymphopenia in 33% [14]. In the phase 3 setting for B-ALL grade 3-4 adverse events were more common in the control chemotherapy arm, however CRS was seen in 4.9% of the blinatumomab treated patients, and infusion reactions were seen in 3.4%. Treatment interruption was required per protocol for 32% of patients overall, including 7% for infections, 6% for neurologic events, 5% for the cytokine release syndrome, 3% for infusion reactions, and 3% for neutropenia compared to 6% for chemotherapy. Due to an OS benefit the trial was stopped early at interim analysis. Grade three neurologic events or higher were similar between the BiTE and chemotherapy arms [15]. Other series have shown toxic neuropathy in nearly twenty percent of patients [16]. Notably, responders may have neurologic events or CRS, necessitating blinatumomab cessation, however it appears safe to rechallenge [11]. Low grade neurologic symptoms are common (21 of 45 patients), however serious neurologic toxicity is rare with just 3 of 45 patients suffering from grade three events. Serious toxicities were aphasia, hemiplegia, and depressed level of consciousness, however only one patient needed treatment interruption and no grade 4 or 5 neurologic symptoms seen [10].

1.2. Checkpoint inhibition

The foundational work for clinical blockade of immune inhibitory signals began over twenty years ago with the discovery in 1994 that CTLA-4 is negative regulator of T-cell activation [17]. Several years later blockade of CTLA-4 was found to enhance anti-tumor activity [18]. By the early 2000s it was known that blockade of PD-1 reversed T cell exhaustion [19]. Clinical trials in melanoma patients in 2010 showed an improved survival with anti-CTLA-4 therapy [20] leading to ipilimumab approval in 2011, followed by PD-1/PD-L1 inhibitor approvals in 2014. By 2015 there were more than 150 clinical trials using checkpoint blockade in many cancers and numerous approvals have been garnered since [21]. These agents have largely been limited to use in solid tumors with many hypothesizing that response appears to correlate with mutational burden which is generally lower in hematologic malignancies [22,23]. Toxicities of these agents has recently been extensively reviewed [24].

There are several areas where checkpoint inhibitors are gaining traction. Classical Hodgkin's lymphoma is characterized copy number alterations at 9p24.1 leading to overexpression of PD-1 ligands. Use of the PD-1 inhibitor nivolumab for relapsed or refractory Hodgkin's has shown impressive response rates in two thirds of patients with only minimal toxicity (Grade 3 neutropenia in 5%, increased lipase in 5%, and fevers in 4% of patients) [25].

Some preclinical data has suggested that CLL patients utilize PD-1 pathway to inhibit immune surveillance leading to Richter's transformation [26]. Twenty-five patients treated with pembrolizumab after progression on ibrutinib (9 of 25 of which had undergone Richter's transformation) were treated finding 4 of 9 transformed patients responding and none of the untransformed CLL patients responding. 60% of patients reported grade 3 or above adverse events which were largely hematologic (thrombocytopenia, anemia, or depressed neutrophil count) as well as dyspnea, fatigue, neutropenia fever, hypoxia [27]. In a trial of both B and T cell lymphoma, as well as multiple myeloma, nivolumab resulted in an impressive objective response rate of 40% with common grade three and four adverse events being pneumonitis (4%), anemia (4%), leukopenia (4%) which is comparable to side effects in solid tumor patients [28].

Preclinical data has evaluated targeting PD1 simultaneously with CAR T (or simply knocking down PD1 [29]) and has shown efficacy in the preclinical setting [30]. Patients failing to respond to CAR-T therapy have been treated with simultaneous PD-1 inhibitors with success and trials are ongoing [31–33]. Given the overlapping and likely synergistic toxicities of these agents, caution will certainly be needed.

1.3. Chimeric antigen receptor T cells

Adoptive cellular therapy via manipulation of autologous or allogeneic T cell to express a chimeric antigen receptor (CAR) has resulted in tremendous success in patients that have very poor outcomes historically. In 2017 two FDA approvals were granted in this space with axicabtagene ciloleucel (Yescarta) for relapsed large-B-cell lymphomas based on ZUMA1 [34] as well as tisagenlecleucel (Kymriah) for relapsed refractory B-cell ALL in those under age 25. While highly successful, these therapies also have the potential for life threatening toxicities, the most serious of which are CRS, neurotoxicity, and HLH/MAS. A description of the mechanisms and