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Immune Modulation in Hematologic Malignancies

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Abstract

The therapeutic potential of the immune system in the context of hematologic malignancies has long been appreciated particularly due to the curative impact of allogeneic hematopoietic stem cell transplantation. The role of immune system in shaping the biology and evolution of these tumors is now well recognized. While the contribution of the immune system in anti-tumor effects of certain therapies such as immune-modulatory drugs and monoclonal antibodies active in hematologic malignancies is quite evident, the immune system has also been implicated in anti-tumor effects of other targeted therapies. The horizon of immune-based therapies in hematologic malignancies is rapidly expanding with promising results from immune-modulatory drugs, immune-checkpoint blockade and adoptive cellular therapies, including genetically-modified T cells. Hematologic malignancies present distinct issues (relative to solid tumors) for the application of immune therapies due to differences in cell of origin/developmental niche of tumor cells, and patterns of involvement such as common systemic involvement of secondary lymphoid tissues. This article discusses the rapidly changing landscape of immune modulation in hematologic malignancies and emphasizes areas wherein hematologic malignancies present distinct opportunities for immunologic approaches to prevent or treat cancer.

Distinct aspects of hematologic malignancies as relevant to immune-modulation

In recent years, immunomodulatory approaches have attracted much attention in solid tumors. In this review, we discuss key aspects of the emerging field of immunomodulation, as they apply to hematologic malignancies. Hematologic malignancies are a diverse group of at least 30 different tumor types, each with distinct biology, pathogenesis and clinical behavior. When considering the cross-talk between malignancy and the immune system, it is

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useful to classify hematologic tumors based on cell of origin, into those that involve multi-potent stem cells (such as acute leukemias), and those (such as lymphoma, myeloma) wherein the target of transformation is a committed lymphoid or myeloid progenitor/progeny. A practical implication of this distinction is that the former are often characterized by severe cytopenias including normal immune cells, and therefore immune-therapeutic strategies need to first restore normal hematopoiesis or adoptively transfer immune effector cells.

Some aspects of the biology of hematologic malignancies deserve distinct considerations (Table 1). Several hematologic malignancies are characterized by systemic involvement of secondary lymphoid tissues. In some settings, the tumor cells may share the developmental niche with normal immune cells leading to immune-paresis. This is commonly exemplified in B cell malignancies such as myeloma and chronic lymphocytic leukemia with a reduction in normal B/plasma cells and consequently hypogammaglobulinemia. In some tumors, cross-talk with normal immune cells may impact tumor growth and survival more directly as it resembles physiologic cell-cell interactions. An example of the latter may be interactions between dendritic cells and tumor cells, or between certain T cell subsets such as T-follicular helper (T_{FH}) cells and tumor cells^{1,2}. Such interactions may also impact immune therapies. For example, T_{FH} cells are characterized by the expression of programmed-death-1 (PD-1), which is also targeted in immune checkpoint blockade.

Bone marrow involvement is a common feature of hematologic malignancies. Bone marrow represents a distinct immunologic tissue and therefore properties of marrow-resident immune cells are likely to impact immune therapies against these tumors³. From a genetic perspective, hematologic malignancies carry fewer mutations and exhibit lower degree of intracлонаl diversity compared to many solid tumors. These considerations make these tumors attractive targets for therapies targeting selected driver mutations, but the lower mutation load may in principle also translate to fewer neo-antigens and therefore fewer targets for adaptive immune responses. Nevertheless, most hematologic malignancies are highly susceptible to lysis by both innate and adaptive immune cells.

Finally, several hematologic malignancies also represent important models to understand immune-surveillance of human tumors as they are characterized by well-defined precursor states amenable to prospective analysis and the ability to isolate individual tumor/precursor cells and surrounding immune cells. Such serial/prospective studies are typically not feasible in solid tumors because precursor states are resected at initial diagnosis. An excellent example in this regard is monoclonal gammopathy of undetermined significance (MGUS) as a precursor to multiple myeloma (MM).

Immune microenvironment in hematologic malignancies- a dynamic regulator

Several lines of evidence point to an important role for the immune tumor micro-environment (TME) in regulating the growth of hematologic malignancies. For example, prior studies have shown that the immune system has the capacity to recognize the earliest/precursor lesions such as MGUS⁴. Interestingly, naturally occurring response against MGUS

includes antigens commonly expressed on stem cells⁵. However, even in the setting of clinical myeloma, TME contains T cells capable of killing tumor cells^{6,7}. Therefore mechanisms that suppress preexisting immunity are a critical barrier to immune-mediated destruction. As in solid tumors, these pathways include several mechanisms including myeloid-derived suppressor cells (MDSCs), regulatory T cells (Treg), immunosuppressive cytokines and expression of co-inhibitory checkpoints⁸. In addition to mechanisms within the TME that inhibit T-cell function, intra-tumoral macrophages and certain subsets of dendritic cells (DCs) can promote tumor growth and even genomic instability^{9,10}.

Properties of the TME also have a major impact on the outcome in other lymphoid tumors including non-hodgkin lymphoma (NHL) and Hodgkin disease (HD). For example, a T-helper1 (Th1) gene expression profile portends improved survival, while a signature of myeloid cells correlates with adverse outcome¹¹. The importance of TME is particularly evident in HD, wherein the tumor cells constitute only a small minority of the tumor bulk and the degree of infiltration of the tumor by T cells or macrophages has a major impact on prognosis^{12,13}. The prognostic impact of TME likely applies across several genetic subtypes.

The potential importance of immune cross-talk in lymphoid tumors is also supported by the findings of recurrent mutations or genomic alterations in major histocompatibility complex (MHC) or key immune genes including those involved in immune checkpoint blockade, which may promote immune ‘escape’^{14–16}. As lymphoid tumors represent tumors involving the immune cells themselves, it is also likely that some of the interactions between immune cells and tumor cells follow physiologic principles. For example, cross-talk between CD28 on tumor cells and CD80/86 on DCs promotes survival of MM cells¹⁷. Indeed, signaling via the B cell receptor has emerged as an important regulator of lymphomagenesis and target of newer therapies. Understanding the nature of antigens that drive B cell tumors remains an important area of research and may help elucidate their underlying etiology¹⁸.

Several paths to immune-modulation

Allogeneic hematopoietic stem cell transplantation represents perhaps the oldest clinically successful immunotherapy for hematologic malignancies and remains the only curative option for several patients with leukemia. Understanding how to reduce the adverse effects of allo-reactivity (such as graft versus host disease) while preserving anti-tumor graft-versus-leukemia effect remains an area of active research in this field¹⁹. Herein we provide an overview of existing/emerging approaches that depend (at least in part) on harnessing the properties of the patient’s own immune system against their own tumors. These approaches can be broadly classified as immune-modulatory drugs/cytokines, vaccines, monoclonal antibodies, immune checkpoint blockade (ICB)/costimulatory antibodies, and adoptive transfer of genetically modified immune cells including chimeric antigen receptor T (CART) cells. It is also apparent that modulation of the immune system may contribute to anti-tumor effects of other non-immunologic therapies, including kinase inhibitors and epigenetic therapies.

Immune-modulating drugs

Thalidomide was initially studied for its immunomodulatory properties, including the capacity to co-stimulate T cells²⁰ and subsequent discovery of its anti-angiogenic effects prompted its evaluation in cancer. Thalidomide and its analogues, notably lenalidomide and pomalidomide have emerged as highly active agents in several hematologic malignancies, and introduction of these therapies has transformed the clinical outlook in MM over the last decade²¹. Although it is likely that these drugs act by several mechanisms including direct anti-tumor effect and anti-angiogenesis, recent studies have demonstrated the potent capacity of these agents to mediate broad immune activation *in vivo*, including both innate and adaptive immunity^{22,23}. The underlying mechanisms have been recently ascribed to drug-induced degradation of Ikaros via cereblon-E3 ligase complex, which in turn releases the Ikaros-mediated transcriptional repression on immune activation^{24–26}. In other words, these drugs seem to act in a fashion similar to “checkpoint blockade”, albeit via targeting “intracellular brakes”. Immunostimulatory capacity of these agents includes effects on innate lymphocytes such as natural killer (NK) or NK-T cells^{22,27}. This property likely contributes to the capacity of these agents to enhance antibody-dependent cytotoxicity (ADCC)²⁸ and has led to several clinical trials combining these agents and monoclonal antibodies with promising results, such as in combination with rituximab²⁹. This class of agents also provide proof of principle that immune modulation can be achieved by targeting intracellular molecules implicated in dampening the immune response.

Monoclonal Antibodies (mAbs)

mAbs are multifaceted agents that mediate anti-tumor effects by several mechanisms including direct anti-tumor effects, Fc-mediated immunologic effects such as ADCC, complement-mediated cytotoxicity (CMC), and enhanced antigen-presentation³⁰. Rituximab (anti-CD20 mAb) has transformed the management of B cell malignancies. Preclinical studies have indicated that anti-tumor effects of rituximab require the Fc component³¹. Newer antibodies targeting CD20 (Ofatumumab and Obinutuzumab) have also shown clinical activity and received FDA approval for management of CLL patients^{32,33}. Ofatumumab is a humanized antibody that binds to a different CD20 epitope than rituximab and mediates greater ADCC³². Obinutuzumab is a glycoengineered antibody that does not engage CMC, but leads to greater ADCC and direct anti-tumor effects³⁴. In addition to CD20, several other targets are currently being explored in the setting of lymphoma. Although early studies with mAbs in the setting of myeloma were disappointing, two antibodies/targets have shown promise. Elotuzumab targets a molecule SLAMF7, which is expressed on myeloma cells, and at a lower level on NK cells³⁵. Based on high response rates in phase II setting, elotuzumab in combination with lenalidomide and dexamethasone is now in phase III testing³⁵. Daratumumab targets CD38 molecule expressed on myeloma cells, and to a lesser extent on T cells³⁶. Daratumumab is one of the first antibodies to show single agent activity in relapsed/refractory MM and received breakthrough designation from the FDA. Two other mAb-based therapies have activity in hematologic malignancies. Brentuximab vedotin is an antibody-drug-conjugate (ADC) that targets CD30 expressed on Hodgkin Reed Sternberg cells and tumor cells in anaplastic large cell lymphoma (ALCL)³⁷. Based on high degree of clinical activity in relapsed HD, Brentuximab received FDA

approval in this setting. An important emerging class of agents are bi-specific T cell-engaging (BITE) antibodies that promote physical coupling between tumor cells and T cells. Blinatumomab is a BITE antibody targeting CD3/CD19 that has shown clinical activity in patients with acute lymphocytic leukemia (ALL) and received breakthrough therapy designation by the FDA for relapsed/refractory Philadelphia chromosome-negative ALL³⁸. Both ADC and BITE technologies are very active areas of investigation.

Vaccines

Vaccines have the theoretical advantage of more tumor-specific targeting of tumor cells, thereby reducing the risk of autoimmunity. As the clonal immunoglobulin (Ig) made by each B lymphoid tumor represents the most tumor specific target, several studies have targeted the Ig-associated idiotypic determinants to boost tumor-specific immunity in the setting of lymphoma and myeloma. Early phase studies with this approach led to promising results. However, only one of three phase III trials led to improved progression-free survival^{39,40}. The role of idiotype-based vaccination in the setting of rituximab-based therapies remains to be clarified and is being considered for patients with follicular lymphoma achieving complete remission following induction therapy. Several other tumor-associated antigens are being explored. These include cancer-testis antigens, oncoproteins (such as WT1), and stem cell associated antigens (such as SOX2)^{5,41,42}.

An important set of antigens are those derived from tumor-associated mutations⁴³. Dendritic cells are potent antigen-presenting cells and have been utilized to stimulate T cell immunity as well as innate lymphocytes with promising results in early phase studies^{23,44}. Another emerging approach is antibody-mediated targeting of DCs in situ, which needs to be tested in hematologic malignancies⁴⁵. Although several of the vaccine-based approaches were effective at inducing immune responses detected in circulation, the clinical efficacy has been modest. Therefore it is likely that such approaches may need to be combined with strategies that target immune-suppressive elements in the tumor bed. As stem cell transplantation (SCT) has been commonly utilized in the setting of hematologic malignancies, the post-SCT setting may be an attractive clinical setting for vaccines or adoptive transfer, as several of the tumor-associated immune tolerance mechanisms may be transiently disabled at that time⁴⁶.

Immunologic effects of anti-cancer therapies

The possible role of immune system in existing and emerging therapies is now increasingly appreciated. For example, approved therapies such as anthracyclines and bortezomib induce immunogenic death of tumor cells via exposure of heat-shock proteins^{47,48}. In preclinical models, the immune system plays an important role in the anti-tumor effects of alkylating agents, as well as epigenetic therapies commonly utilized against hematologic malignancies^{49,50}. Recent studies have suggested that B cell receptor targeting agents such as Ibrutinib also activate T cells via “off target” effects on ITK⁵¹. Finally, oncolytic virotherapies are now targeting hematologic malignancies and in several instances (as exemplified by measles virus targeting myeloma), the immune system may contribute to anti-tumor effects⁵². While the dominant effect of all of these agents likely involves direct

effects on tumor cells, the contribution of an immune component to their anti-tumor effects provides the basis for combinations with immune-therapies.

Adoptive cellular therapies- genetically modified T cells and beyond

An exciting and rapidly emerging area in terms of immunotherapy of hematologic malignancies is the application of adoptive transfer of immune cells, including chimeric antigen-receptor+ T (CART) cells⁵³. Principles of adoptive cell therapy were based on the success of infusion of donor lymphocytes in recipients of allogeneic stem cell transplant and virus-specific T cells in Epstein-Barr virus-driven lymphomas. Preclinical studies provided evidence for the role of homeostatic cytokines during the lymphopenic phase in promoting the growth and survival of transferred cells and led to incorporation of these strategies in clinical protocols⁵⁴. Several studies are now testing T cells genetically modified to express T cell receptors against tumor antigens or chimeric receptors against cell surface antigens. As expected, a critical issue for these therapies is the choice of the antigen being targeted, as cross-reactivity with antigens expressed on normal cells can be highly problematic⁵⁵. Second-generation CARTs expressing two co-stimulatory molecules have been effective and those with further modifications are now being tested⁵³. CD19-CARTs have emerged as attractive agents in B cell malignancies as CD19 is often expressed on most tumor cells and the expected toxicity of B cell aplasia is manageable^{56–58}.

Early clinical results with CD19-CARTs were based on therapy of patients with relapsed/refractory CLL⁵⁶, which were impressive as they targeted disease refractory to multiple therapies. However the results have been even more impressive in patients with B-ALL, with response rates exceeding 80%, including in children^{59–61}. In several of these studies, CART cells have been utilized as a bridge to transplantation. Further studies are needed to establish the durability of responses as a single agent, and whether long-term persistence of transferred cells is needed for durable responses. Clinical studies of CART cells have thus far been restricted to a few institutions, particularly as the management of potentially life-threatening cytokine-release syndrome can be challenging.

CART therapy is now being extended to other hematologic malignancies. For example, CART cells targeting CD38, CD138, BCMA or SLAMF7 are being investigated in MM⁶². In addition to CART cells, genetically modified T cells expressing TCRs against tumor antigens (such as NY-ESO1) are also being tested in hematologic tumors⁶³. Finally, as recently evaluated in solid tumors, T cells against mutation-derived neoantigens are also ripe for testing in hematologic malignancies⁴³. As discussed earlier, pediatric and hematologic malignancies represent prime candidates for such an approach due to the lack of genomic complexity as typically found in solid tumors.

In addition to T cells, hematologic malignancies are also very sensitive to innate lymphocytes including NK or NKT cells. Evidence for NK-mediated anti-tumor effects has emerged from allogeneic stem cell transplants wherein AML patients were mismatched for killer-cell immunoglobulin-like receptor (KIR) from their donors, which led to enhanced NK cell reactivity due to lack of KIR suppression^{64,65}. Adoptive transfer of NK cells is being attempted in the setting of relapsed leukemia^{66,67}. Lirilumab is an anti-KIR antibody

that has been tested in early phase trials in AML and smoldering MM^{68,69}. In addition to NK cells, other innate lymphocytes have also been targeted in hematologic malignancies with promising results. Tumor cells including those in MM commonly express CD1d and are sensitive to lysis by invariant NKT cells⁷⁰. Tumor progression in MM is associated with NKT dysfunction⁷⁰. This has prompted studies of adoptive transfer of DCs loaded with iNKT ligand α -galactosylceramide to activate NKT cells as well as adoptive transfer of NKT cells in human MM⁷¹.

Immune checkpoint blockade and immune-activating antibodies

As with solid tumors, dampening of T cell function via engagement of co-inhibitory receptors is increasingly appreciated as a mechanism of T cell dysfunction and immune escape in the tumor bed⁷². Several pathways including PD1/PD-L1, Tim3, Lag-3 and BTLA have been implicated in suppressing T cell immunity in hematologic malignancies⁷³. Expression of PD-L1 on tumor cells as well as associated antigen presenting cells is a common feature of several hematologic malignancies such as MM, leukemia and lymphoma, and is thought to be driven by diverse mechanisms, including cytokines such as interferon- γ in MM or genetic changes such as amplification of 9p24 in HD tumor cells^{15,73,74}. Although prospective studies correlating the expression of inhibitory molecules with clinical outcome are lacking, the preclinical data provide strong rationale for targeting these checkpoints in hematologic malignancies. Initial studies of immune checkpoint blockade in hematologic malignancies with anti-CTLA4 mAb (ipilimumab) evaluated patients with refractory lymphoma and in the setting of relapse for allogeneic transplant^{75,76}.

More compelling evidence for potential benefit from checkpoint blockade has emerged from studies targeting the PD-1 pathway⁷³. The first anti-PD1 antibody tested in hematologic malignancies was pidilizumab. In a phase II trial in patients with relapsed/refractory diffuse large B cell lymphoma, pidilizumab following autograft led to an objective response rate (ORR) of 51% with complete remission (CR) in 34% of patients⁷⁷. Combination of pidilizumab and rituximab also led to interesting clinical activity in a small phase II trial of patients with follicular lymphoma (ORR 66%, CR 52%)⁷⁸. More recently, higher affinity anti-PD-1 antibodies such as nivolumab and pembrolizumab, which were developed initially in solid tumors, have been tested in lymphoid malignancies, with evidence of single agent activity in patients with both NHL and HD^{79–82}. The results for single agent activity of PD-1 blockade are most impressive in the setting of relapsed HD, including ORR 87% (CR17%) with nivolumab and ORR 53% (CR20%) with pembrolizumab^{81,82}. Nivolumab was granted breakthrough designation by the FDA for therapy of HD after failure of stem cell transplant and brentuximab. Nivolumab also produced objective responses in 36% of patients with diffuse large B cell lymphoma and 40% of patients with follicular lymphoma⁷⁹. Several other antibodies targeting PD-1/PD-L1 pathway are entering clinical testing in hematologic malignancies, both as single agents and in combination with other therapies. Results of these ongoing investigations are eagerly awaited. However it now seems likely that combinations based on immune checkpoint blockade may occupy increasing role in the immunotherapy of hematologic malignancies. As with solid tumors, there is an unmet need for biomarkers to identify patients most likely to benefit from these therapies and identify optimal checkpoint targets or combinations. Recent studies

demonstrate that immunologic as well as clinical effects of such combinations may be distinct from blockade of individual checkpoints^{83,84}.

In addition to therapies that block co-inhibitory molecules, agonistic antibodies that enhance immune effector cells are also of interest. It is possible that these antibodies may have distinct toxicity profiles, as evidenced by hepatotoxicity observed in early clinical trials targeting CD137⁸⁵. Thus far, most of the studies targeting these agents have focused on solid tumors, although preclinical studies also provide a rationale for targeting hematologic malignancies. For example, in lymphoma models, agonistic anti-CD137 antibodies were found to synergize with rituxumab via enhanced ADCC^{86,87}.

Summary and future directions

Therapeutic potential of the immune system against hematologic malignancies has long been appreciated due to the curative impact of allogeneic stem cell transplantation. Hematologic malignancies present several distinct considerations relative to solid tumors for application of immune-modulation. Recent advances in cancer immunology have ushered in a new era with a growing arsenal of several immune-based therapies showing promising clinical activity against hematologic malignancies. Although there are examples of success stories in all categories, much of the recent excitement relates to the promise of ICB and CART therapies.

It is likely that many of these will need to be tested in combination with other existing agents. Integrating these therapies in the clinical management of patients may help realize the potential of the immune system to prevent or treat hematologic malignancies.

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Table 1

Some distinct considerations for immune-modulation in hematologic malignancies

Property of hematologic malignancies	Implications
Common involvement of secondary lymphoid tissue	Differences in chemokine requirement for T cell infiltration into tumor tissue
Shared niche with normal lymphoid cells (lymphoid tumors)	Immune paresis
Hematopoietic stem cell involvement (e.g. acute leukemia)	Cytopenias
Role of physiologic interactions with other immune cells due to immune cell of origin	e.g. T _{HH} -B cell interactions may promote tumor growth
Bone marrow involvement	Marrow as a distinct immune tissue
Susceptible to both adaptive and innate lymphocytes	Targets for both innate and adaptive immunity
Precursor states (e.g. MGUS) unresectable	Models to study immune-surveillance
Less mutational complexity (compared to most solid tumors)	? more amenable to personalized immunotherapy