



Immunologic treatment strategies in mantle cell lymphoma: checkpoint inhibitors, chimeric antigen receptor (CAR) T-cells, and bispecific T-cell engager (BiTE) molecules

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Abstract: Over the past 10–15 years, there has been a surge in the development and utilization of immunologic strategies aimed at harnessing the power of the cellular immune system to treat a remarkable range of human disease. As is being seen throughout the spectrum of malignant hematology, there are several emerging immunologic therapies which may ultimately revolutionize the treatment and clinical outcomes of patients with mantle cell lymphoma (MCL). Three unique immunologic approaches—checkpoint inhibitors, chimeric antigen receptor (CAR) T-cell therapy, and bispecific T-cell engager (BiTE) molecules—are currently on the forefront of clinical investigation. While preclinical studies have suggested a mechanistic role for immunomodulation via checkpoint blockade (PD-L1, PD-1) in patients with MCL, clinical data thus far suggests only modest success. CAR T-cell therapies, engineered to directly overcome deficiencies in the anti-tumor T-cell response, appear to show early promise and large trials actively enrolling MCL patients are currently in progress. BiTE molecules, which seek to engage and directly activate the cytotoxic power of T-cells upon bispecific interaction with tumor antigen, are being explored in treatment of MCL and early efficacy data seems encouraging as well.

Keywords: Lymphoma; mantle cell lymphoma (MCL); non-Hodgkin lymphoma (NHL); immunotherapy; checkpoint inhibitor therapy; chimeric antigen receptor T-Cell therapy (CAR T-Cell therapy); bispecific T-cell engager molecules (BiTE molecules); bispecific

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Introduction

Basics of T-cell immunity

There are several emerging immunological approaches to the treatment of patients with mantle cell lymphoma (MCL). In order to understand these unique approaches, it is crucial to first appreciate the fundamental components of an effective T-cell mediated immune response.

In general, an effective T-cell response to antigens is characterized by three key steps: recognition, activation, and

persistence (1). In antigen “recognition,” the T-cell receptor (TCR) recognizes an APC-presented antigen (peptide-MHC antigen), forming the T-cell-antigen-receptor complex. This T-cell-antigen-receptor complex delivers an initial “activation” signal, referred to as “signal 1.” In response, the presenting APC expresses costimulatory molecules which bind to costimulatory receptors present on T-cells, a process referred to as “signal 2.” The persistent combination of both antigen recognition and costimulation (signal 1 + signal 2) ultimately leads to the

robust production of “activated” T-cells. When this process occurs in a population of naïve T-cells, the result is clonal expansion and differentiation into effector T-cells. When occurring in already differentiated populations of effector T-cells or memory T-cells, the result is performance of effector T-cell function (i.e., cytokine secretion, target cell killing, etc).

Alternatively, it is also important to understand the underlying processes which may lead to the production of unresponsive or inactivated T-cells. There are two primary ways in which this may occur, both of which occur after the initial “signal 1” process outlined above. First, in a process known as “coinhibition,” rather than a costimulatory “signal 2” process, coinhibitory molecules presented by APCs may bind to coinhibitory receptors present on T-cells. Of note, even in the presence of an effective costimulation signal, the process of coinhibition may still occur if the coinhibitory signal dominates or out-competes the costimulatory signal. In a second process, most often involving an immature or poorly activated APC, the coactivation “signal 2” is never effectively established. In both cases, the end result is production of either unresponsive (anergic) T-cells or T-cell apoptosis.

Inadequate T-cell response in MCL

Several mechanisms have been proposed to account for the presence of an inadequate T-cell response in patients with lymphoma. While “lymphomas” are in reality a vastly heterogeneous group of malignancies which arise from developing lymphocytes, broadly speaking, there are three chief categories into which these mechanisms are generally characterized: loss of typical antigen presentation, suppression of activated cells, and the presence of additional suppressive ligands (2). Furthermore, while approximately 90% of all lymphomas arise from B cell lineage (MCL, being among them), there are of course important ramifications with regard to underlying deficiencies in the normal T-cell response which ultimately allows for the sustained proliferation of aberrant B lymphocytes necessary to create a lymphoma.

With regard to MCL in particular, we are currently aware of several unique aberrations identified in the preclinical setting which may contribute to an inadequate underlying T-cell response in these patients. First, in a cohort of 17 unique MCL patients and two defined MCL cell lines, Khodadoust *et al.* have identified the presence of MCL-specific MHC-I and MHC-II epitopes (3) as well

as characterized a pattern of abnormal cytolytic activity among neoantigen-specific CD4 T-cells which appears unique to patients with MCL.

Second, Yang *et al.* have demonstrated that T-cells in MCL patients appear to inhibit the production of anti-tumor cytokine CD4 + CD25 through interaction between PD-1 and PD-L1 (4). Of note, as is the case with most subtypes of B cell NHL, several groups have reported the overall lack of expression of both PD-1 (5-7) as well as PD-L1 (7,8) on malignant B cell populations in patients with MCL. However, Wang *et al.* have demonstrated that, when present, the expression of B7-H1 (PD-L1) on MCL cells is able to effectively inhibit T-cell proliferation induced by the tumor cells, impair the generation of antigen-specific T-cell responses, and ultimately render the tumor cells resistant to T-cell-mediated cytotoxicity (9). Furthermore, this study demonstrated (both *in vitro* and *in vivo*) that blocking or knocking down B7-H1 on MCL cells effectively enhances T-cell responses and restores tumor-cell sensitivity to T-cell-mediated killing. As will be further detailed below, with the advent of immunomodulatory therapies, the expression profile of PD-1 and/or PD-L1 of a given malignancy has growing implications with regard to immunotherapeutic targeting and efficacy within the clinical setting.

In addition, as will be outlined further below, T cells themselves are now being increasingly utilized for their cytotoxic effect as anti-tumor therapies directed against malignancies which arise from aberrant immune cells, such as lymphomas. As a proof-of-concept in the setting of MCL, allogeneic SCT has been shown to be an effective treatment modality in these patients (10), further underlying the notion that T cells in principle are indeed able to mediate effective cytotoxicity against malignant MCL cells.

Three key immunologic treatment strategies in MCL

Immunomodulation: checkpoint inhibition

Over the past 10–15 years, there has been a surge in the development of “immunomodulatory” strategies aimed at treating a remarkable range of human disease (including cancer, infection, autoimmunity, transplant rejection, and more). As a brief overview, immunomodulatory “biologics” are molecules designed to engage and interact with cell surface signaling molecules present on host immune cells, thereby influencing the direction and/or magnitude of the

lymphocyte response (11). In conditions characterized by hyper-activity of the host immunologic state (i.e., transplant rejection, autoimmunity), such molecules are used to dampen excessive hyper-proliferation of immune cells, thus blunting their resultant activity. In conditions which persist at least partly due to evasion and/or inadequacy of the host immune response (i.e., malignancy, infection), these molecules are utilized to stimulate, sensitize, and/or enhance the immunologic state.

Such cell surface molecules targeted in immunomodulation include those involved in the co-signaling pathway (i.e., co-stimulatory and co-inhibitory signals created through the interaction of T-cells and APCs, as outlined above) as well as membrane receptors involved in intercellular adhesion and migration. Generally speaking, the molecular targets exploited in immunomodulatory therapies are grouped into two major gene families: the immunoglobulin (Ig) superfamily and the tumor necrosis factor (TNF)–TNF receptor (TNFR) superfamily.

Among Ig molecules, the B7 (B cell, APC)–CD28 (T-cell) family members have crucial roles in modulating the outcome of lymphocyte-mediated immune responses (12). When upregulated on a given cell, B7-H1—a B7 family member later renamed PD-L1 for its interaction with the receptor PD-1 on T-cells—has been shown to allow for effective evasion of the host immune system (13). Mechanistically, this is thought to occur primarily through a signal—when propagated by proper engagement of PD-L1 with PD-1—which inhibits further TCR-mediated activation of IL-2 production and T-cell proliferation, thus allowing host cell evasion of T-cell mediated destruction (14). This interaction is, now famously, referred to as an immune system “checkpoint,” serving as a sort of screening process in place to prevent excessive T-cell mediated destruction of otherwise healthy host cells. Classically, the term “checkpoint inhibition” refers to the therapeutic use of molecules designed to inhibit this interaction, thus preventing further target cell evasion of proper T-cell mediated destruction (i.e., the “unmasking” of a targeted cancer cell which has effectively upregulated PD-L1 and/or PD-1 expression to suppress the T-cell mediated checkpoint system).

As mentioned previously, while PD-1/PD-L1 expression is not typically a feature observed in the malignant B cell populations of patients with MCL, there is *in vitro* and *in vivo* evidence for PD-L1 inhibition as a mechanism for effective enhancement of the T-cell response and T-cell-mediated killing of tumor cells in MCL patients with

tumor cells found to be positive for PD-L1 expression (9). With this in mind, there has been optimism from the field at the possibility of exploiting this feature through the use of checkpoint inhibitor therapies in select patients with MCL. Furthermore, there are notable success stories with such strategies among patients with other forms of lymphoma. For example, in classic Hodgkin’s lymphoma, alterations in chromosome 9p24.1 are known to increase the abundance of PD-L1 and PD-L2. This mechanism has been successfully exploited on the clinical stage, as PD-1 blockade with Nivolumab (15) as well as Pembrolizumab (16) has demonstrated substantial and sustained therapeutic activity as well as acceptable safety profile across a broad spectrum of patients with relapsed or refractory Hodgkin’s lymphoma (17).

However, attempts to apply PD-1 blockade broadly to patients across several subtypes of non-Hodgkin’s B-cell lymphoma, including MCL, has thus far resulted in a wide variability of disease response (18). Lesokhin *et al.* have conducted a phase I trial of Nivolumab in patients with a variety of refractory B cell lymphoma subtypes. Four patients with MCL were included among the patients enrolled in this trial. While there were no differences in toxicity observed among the MCL patients when compared to those with other B cell malignancies, a significant therapeutic response was unfortunately not observed in the MCL patients, with 3 of the 4 patients experiencing “stable disease” as the best response. In addition, 3 of the 4 patients were found to have negative expression of PD-L1 and PD-L2 (the remaining patient had just 5% PD-L1 positivity). As mentioned previously, others have proposed that the low expression of PD-1 and PD-L1 often observed in MCL may underscore the lack of clinical response rates to PD-1/PD-L1 blockade (7).

In summary, preclinical studies suggest a potential role for PD-L1 inhibition as a mechanism for enhancement of the T-cell response and T-cell-mediated killing of tumor cells in select patients with MCL. Unfortunately, while clinical data is currently limited to just a handful of patients, early studies have not yet demonstrated immunomodulation through immune checkpoint blockade as a clinically successful strategy among patients with MCL.

Chimeric antigen receptor (CAR) T-cells

As has been outlined above, cancer cells contain many features which enable them to evade destruction by the T-cell mediated immune system. Furthermore, we

now know that cancer cells help promote a surrounding microenvironment which inherently suppresses T-cell activity, survival and migration. The genetic engineering and enhancement of T-cells themselves—known as CAR T-cells (19)—is being increasingly utilized in the clinical setting to overcome these multifactorial challenges. In this process, T-cells are taken from the blood of cancer patients and then modified with genes which encode for receptors aimed at recognizing cancer-specific antigens (20). Additional genes can be included to enable resistance to immunosuppression, extend survival and enhance the penetration of engineered T-cells into tumor cells themselves.

Much has been learned through the early stages of clinical experience with CAR T-cell therapies. The first iterations (First Generation, 1G) CAR T-cell therapies demonstrated disappointingly poor *in vivo* persistence and efficacy. This was attributed to insufficient receptor costimulation, which has been overcome in later generations through the subsequent additions of a CD28 costimulatory endodomain to the CAR backbone (2G) and a second costimulatory endodomain from OX40 or 4-1BB (3G). These modifications have greatly improved the *in vivo* persistence and anti-tumor efficacy of these agents, however along with increased efficacy important safety concerns have arisen out of clinical trials (21).

In an early clinical trial of “3G” CAR T cell therapy, an observable clinical response was observed in all four patients (three patients with relapsed MCL and one with follicular lymphoma) receiving CD20-directed CAR T-cell infusions (CD20-specific CAR with CD28 and 4-1BB costimulatory domains) (22). Two of the three MCL patients enrolled in the study received all planned T-cell infusions after cyclophosphamide lymphodepletion. The clinical results were promising, and the two MCL patients receiving full therapy remained free of progression for 12 and 24 months (of note, median time to progression for relapsed MCL in most clinical trials conducted at the time of this study was approximately 6 months). From a safety standpoint the therapy was well-tolerated, although one patient developed transient infusional symptoms.

In addition, several clinical trials with CD-19 directed CAR T-cells have enrolled refractory MCL patients, with mixed results. Thus far, three separate trials have demonstrated measurable clinical responses in 0 of 4 (23), 1 of 2 (24), and 1 of 2 (25) MCL patients, respectively. Following FDA breakthrough designation, there are several active clinical trials with CD-19 directed CAR

T-cell therapies currently enrolling MCL patients (*Table 1*). Among them are KITE-C19-ZUMA-2 (26) (a phase II, multicenter, open-label trial with a goal of enrolling 70 R/R MCL patients who have progressed on prior chemotherapy, an anti-CD20 antibody, and a BTK inhibitor) and TRANSCEND NHL 001 (27) [a phase I, open-label, multi-center trial with a goal of enrolling 274 patients to evaluate the safety, PK, and antitumor activity of modified T cells (JCAR017) in adult patients with relapsed or refractory B-cell NHL]. Without question, the outcome of these studies will be paramount in shaping the role of CAR T-cell therapies for the treatment of MCL patients going forward.

In summary, CAR T-cells directly overcome deficiencies in the host anti-tumor T-cell response through the genetic engineering and enhancement of a patient's own T-cells. Although clinical data is currently limited to just a handful of patients with MCL, CAR T-cell therapy appears to represent a promising future option for MCL patients and several trials are actively enrolling patients at this time.

Bispecific T-cell engager (BiTE) molecules

Another immunologic approach to the treatment of MCL comes in the form of bispecific T-cell Engager, or “BiTE” molecules. These molecules, such as Blinatumomab (MT103), are constructed to directly recruit T cells in a fashion that is independent of peptide antigen presentation by tumor cells (28). BiTE antibodies are designed to both physically link T cells and tumor cells as well as trigger the signalling cascade of the TCR by binding directly to the CD3 component of the receptor. Through this mechanism, any antigen-experienced cytotoxic T cell can be “engaged” and directed against a given tumor cell. However, as a safety mechanism, the bispecific design inherently limits over-activation as T cell recruitment and subsequent activation is only initiated when the second arm of the BiTE antibody is bound to its target antigen on the tumor cell surface. Sole binding of the BiTE antibody to T cells will not cause T cell activation.

Regarding the clinical efficacy of BiTE molecules in patients with MCL, one early phase I study has shown encouraging results, with 5 of 7 MCL patients enrolled in the study demonstrating significant treatment response following administration of blinatumomab (29). In addition, a recent phase I trial of REGN1979—a CD20xCD3 bispecific antibody based on an IgG4 isotype modified to reduce Fc binding—has demonstrated durable response in 1

Table 1 Active immunotherapy clinical trials for MCL patients in the USA and Europe

Modality	Title	Intervention	Location
Immunomodulatory (anti PD1/PD-L1)	Phase I/II study of pembrolizumab in patients failing to respond to or relapsing after anti-CD19 chimeric antigen receptor modified T-cell therapy for relapsed or refractory CD19+ lymphomas	Pembrolizumab	Pennsylvania, USA
	Pembrolizumab and ibrutinib in treating patients with relapsed or refractory non-Hodgkin lymphoma	Pembrolizumab + Ibrutinib	Ohio, USA
	Nivolumab and lenalidomide in treating patients with relapsed or refractory non-Hodgkin or Hodgkin lymphoma	Nivolumab + Lenalidomide	Ohio, USA
	Dendritic cell therapy, cryosurgery, and pembrolizumab in treating patients with non-Hodgkin lymphoma	Pembrolizumab	Minnesota, USA
CAR T-cell	A phase I/II study to evaluate the safety of cellular immunotherapy using autologous T cells engineered to express a CD20-specific chimeric antigen receptor for patients with relapsed or refractory B cell non-Hodgkin lymphomas	anti-CD20 CAR T-Cell therapy	Washington, USA
	Treatment of patients with relapsed or refractory CD19+ lymphoid disease with T cells expressing a third-generation CAR	anti-CD19 CAR T-Cell therapy	Heidelberg, Germany
	A phase 2 multicenter study evaluating subjects with relapsed/refractory mantle cell lymphoma	anti-CD19 CAR T-Cell therapy: KTE-C19	Multi-site, USA
	Genetically modified T-Cell therapy in treating patients with advanced ROR1+ malignancies	ROR1 CAR-specific autologous T-lymphocytes	Washington, USA
	Laboratory treated T cells in treating patients with relapsed or refractory chronic lymphocytic leukemia, non-Hodgkin lymphoma, or acute lymphoblastic leukemia	Autologous Anti-CD19CAR-4-1BB-CD3zeta-EGFRt-expressing T Lymphocytes	Multi-site, USA
	CAR T-cell receptor immunotherapy for patients with B-cell lymphoma	Anti-CD19-CAR PBL	Maryland, USA
	Study evaluating the safety and pharmacokinetics of JCAR017 in B-cell non-Hodgkin lymphoma (TRANSCEND-NHL-001)	JCAR017 Modified T Cells	Multi-site, USA
BiTE molecule	Study to evaluate the safety, tolerability, pharmacokinetics, and efficacy of AMG 562 in subjects with r/r diffuse large B-cell lymphoma, mantle cell lymphoma, or follicular lymphoma	AMG 562	California, USA; Leuven, Belgium

of 3 MCL patients enrolled in the study (30).

In summary, T-cell activation is directly achieved with BiTE molecules in MCL, and clinical efficacy—although early with limited data available—seems encouraging.

Summary

As is being seen throughout the spectrum of malignant hematology, while data is currently limited, there are several emerging immunologic therapies which may ultimately

revolutionize the treatment and clinical outcomes of patients with MCL. Three unique immunologic approaches—checkpoint inhibitors, CAR T-cell therapy, and BiTE molecules—are currently on the forefront of clinical investigation. While preclinical studies have suggested a mechanistic role for immunomodulation via checkpoint blockade (PD-L1, PD-1) in patients with MCL, clinical data thus far suggests only modest success. CAR T-cell therapies, engineered to directly overcome deficiencies in the anti-tumor T-cell response, appear to show early

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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