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Review Article

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Potentiation of Efficacy of Chimeric Antigen Receptor (CAR) T-cell Therapy in Hematological Malignancies using FDA-Approved Small Molecule Sensitizing Agents

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Abstract

Chimeric antigen receptor CD19 CAR T-cell therapy has received FDA-approval for treatment of B cell malignancies. CD19 is an ideal target for B cell malignancies due to its limited expression by B lineage cells. Non-Hodgkin's Lymphoma of B-cell origin (NHL B-cell) accounts for about 4% of all cancers in the United States. Traditionally, combination chemotherapy consisting of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) was considered as standard treatment option for NHL patients. However, a subset of individuals was inherently resistant to CHOP or developed resistance upon continued exposure to chemotherapy. The development of drug-resistance, plus the undesired toxic side effects of this regimen, led to the inclusion of anti-CD20 mAb, Rituximab, to chemotherapy protocols of NHL patients (R-CHOP). Superior improvement was observed in patients undergoing R-CHOP compared to CHOP. More recently, chimeric antigen receptor (CAR) T-Cells redirected against CD19 (CD19 CAR T-cell) has proven to be an effective immunotherapy against various cancers including NHL. Despite initial success, and like other approaches, NHL patients become unresponsive to CD19 CAR T-Cells due to selective outgrowth of NHLs with deregulated expression of apoptotic proteins. Histone deacetylase inhibitors (HDACis) and celecoxib have gene regulatory effects and skew the tumor intracellular environment into a proapoptotic milieu. Thus, resistant NHL cells will become sensitized to apoptotic death signals delivered by CD19 CAR T-Cells. We propose the inclusion of FDA-approved small molecules as sensitizing agents to reduce the apoptosis threshold of resistant NHL and boost CD19 CAR T-cell efficacy.

Introduction

Traditional treatment options for patients with Non-Hodgkin's Lymphoma (NHL) includes radiation or combination chemotherapy using cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). However, some patients were inherently resistant to CHOP or developed resistance upon continued chemotherapy administration. Also, CHOP proved to be very toxic to the patients. Development of resistance to CHOP, plus the undesired toxic side effects of this regimen, led to the inclusion of chimeric mouse anti-human CD20 monoclonal antibody (mAb), Rituximab, to chemotherapy protocols of NHL patients (R-CHOP). Superior improvement was observed in patients undergoing R-CHOP compared to CHOP. Patients undergoing R-CHOP treatment demonstrated 46% to 50% improvement, however, patients developed resistance to this modality, necessitating the need for alternative therapeutic approaches [1].

Chimeric Antigen Receptors (CARs), redirect patient's autologous lymphocytes to tumor associated antigens (TAA), consist of the Ag recognition portion of a mAb fused to an intracellular signaling domain able to activate T-Cells, thus, providing non-MHC restricted Ag recognition. CARs effectively target and destroy tumors when expressed in $CD8^+$ Cytotoxic T Lymphocytes (CTL), Natural Killer (NK) cells, neutrophils, and monocytes [2-4]. CAR constructs containing more than one activation moiety enhance T-Cells activation, being the association of the CD28 co-stimulatory molecule to CD3ζ signaling motif the most commonly used, constituting the 2^{nd} (CD3ζ and one co-stimulatory moiety) and 3rdgeneration (CD3ζ and 2 co-stimulatory moieties) CARs [5,6]. CD19 is an ideal target for immunotherapy because it is only expressed in B cell lineages, but not on hematopoietic stem cells; is present in most of the leukemia and lymphomas. As experienced with Rituximab,

humans can survive after ablation of B-lymphocytes with periodical infusions of Immunoglobulin (Ig). CD19-specific CARs effectively target $CD19^+$ hematological malignancies *in vitro and in vivo.* Currently, clinical trials are being conducted with adoptively transferred modified mature T-cells, but the effector cells are only transiently present, which limit treatment efficacy [3-8].

Patients with recurrent B-lineage malignancies have greater than 50% chance of cure, despite prior intensive therapy. Novel strategies are needed to improve morbidity and mortality of those patients. Current data support that CD19-specific CAR effectively redirects immune effector cells to eradicate B-lineage cancers, but persistence of effector cells is a major limitation to clinical applications allowing malignancy to recur [3-8]. Another major limitation of modern cancer immunotherapeutic approach is the development of resistance through inherent or acquired anti-apoptotic mechanisms by tumors.

Small Molecule Sensitizing Agents Celecoxib and Histone Deacetylase Inhibitors

Regulation of Apoptotic Machinery in Non-Hodgkin's Lymphoma (NHL) by Celecoxib (Cox-2 inhibitor): Role in Tumor Immunity.

Increased expression of cyclooxygenease-2 (Cox-2), a key regulator of inflammation, is often observed in hematological malignancies, which correlates with poor patient prognosis [9]. Data from phase II clinical trials show high-dose Cox-2 inhibitor (Celecoxib) is well-tolerated in patients with relapsed or refractory aggressive NHL with minimal toxicity profile [10]. Celecoxib significantly prolongs survival of nude mice harboring intracranial lymphoma and is effective against B lymphoma *in vivo* [11, 12]. Celecoxib induces tumor cell death via a Bcl-2-independent, apoptosome-dependent, intrinsic apoptotic pathway involving mitochondria [13]. Cox-2 inhibitory function is not required for cytostatic and apoptotic effects of Celecoxib. In fact, inhibition of cell proliferation due to down-regulation of cyclins A and B and loss of cyclin dependent kinase (CDK) activity is reported in *in vitro and in vivo* models of Burkitt's lymphoma treated with dimethyl-celecoxib (DMC), a Celecoxib analog lacking Cox-2 inhibitory function [14]. In KSHV and EBV related lymphomas and primary AML cells, Celecoxib induces synergistic cytostasis and apoptosis in combination with bortezomib, eicosonoid receptor antagonists, and doxorubicin, by triggering ER stress, cyclin E and CDK2 down-regulation, G0/G1 arrest, and survivin down-regulation [15-17]. In lymphoma, $Bcl\text{-}_{xL}$ and Mcl-1, but not Bcl-2, form a high affinity complex with Bak, and block apoptosis [18]. Celecoxib, via Mcl-1 down-regulation, disrupts this loop and induces apoptosis [19]. In Bax deficient lines, loss of Bak confers complete Celecoxib-resistance [20]. Celecoxib also blocks AKT/GSK3β survival pathway in HTLV-induced leukemia and induce apoptosis via intrinsic pathway independent of Bcl-2 and $Bcl\text{-}_{xL}$ [21].

Regulation of Apoptotic Machinery in Non-Hodgkin's Lymphoma (NHL) by Histone Deacetylase Inhibitor (HDACi): Role in Tumor Immunity.

HDACis remodel chromatin structure, and consequently, activate gene expression. However, HDACi influence the behavior and survival of tumors by diverse mechanisms, including promoting expression of differentiation- or death-inducing genes while down-regulating the expression of prosurvival genes, thus, generating an intracellular pro-apoptotic milieu [22]. HDACi-induced transcriptional activation causes increased surface expression of death receptors, MHC molecules, tumor Ags recognized by CTL, NK ligands recognized by NKG2A [23-26]. Epigenetic modifiers render tumors more recognizable by the immune system; HDACi increase anti-tumor activity of ACT, enhance cytotoxic potential of CTLs against tumors and combined with IL-2 have synergistic tumoricidal activity [27-29].

Notably, HDACi selectively target tumors and induce pro-apoptotic transcriptional responses, thus, could potentially be used as immune sensitizers [30,31]. As single agent, HDACi is approved in the treatment cutaneous T-cell lymphoma and peripheral T-cell lymphoma, has anti-tumor activity in lymphoma via modulation of survival/ anti-apoptotic signaling pathways, and reverses malignant phenotype in preclinical models [22,32-37]. Because of the pleiotropic effects of HDACis and Celecoxib, their combination with other anti-cancer modalities, particularly immunotherapy, represents a promising research opportunity. Further insights into their mechanism of action will allow optimization of this approach, and will expand their future usage in other cancers. The above data provide strong rationale for studying the underlying mechanism of CD19CAR CTL-resistance in NHL and understanding the mechanism of sensitization by these small molecules with the goal of using them in conjunction with CD19CAR CTL in future trials.

Conclusion

CD19-redirected CAR CTL immune therapy has shown promising results in the clinical trials of patients with NHL B-cell tumors. The modest to low clinical response rates might be due to attainment of various resistance mechanisms by NHL B-cells following initial infusion of CD19 CAR transduced CTLs to avoid apoptotic death signals delivered by CD19 CAR CTL. The underlying molecular mechanism(s) of acquisition of resistance following initial treatment, and approaches to bypass resistance remain indefinable. We have previously reported these matters [38]. To attain a better understanding of potential mechanisms of resistance, and to design means to reverse resistance, we established an *in vitro* model of resistance of human NHL B-cells to CD19 CAR transduced primary human CTLs. We showed that CD19 CAR transduced primary human CTLs kill $CD19^+$ human NHLs in a CD19- and caspase-dependent (using pan-caspase inhibitor (zVAD-fmk)) manner. Significant reduction in NHL killing by caspase inhibitor is a clear indication that CD19 CAR CTLs principally kill $CD19^+$ sensitive NHLs by apoptosis.

Immune effector cells such as $CD8^+$ CTLs and NK cells eradicate tumors primarily via apoptosis induction mediated by four major pathways: TRAIL, FasL, Granzyme, or TNF. Treatment of NHL B-cells with TRAIL antagonistic (blocking) mAb prior to co-incubation with CD19 CAR CTL effector cells significantly reduced their rate of killing suggesting that CD19 CAR transduced CTLs primarily use TRAIL apoptotic pathway in killing sensitive NHL B-cells. We also observed that R-NHL cells developed resistance to recombinant human TRAIL (rhTRAIL) further confirming the role of TRAIL pathway in CD19 CAR CTL-mediated killing of NHL B-cells [38]. Other apoptotic pathways are also possibly operative in CD19 CAR CTLs, however, their contribution warrants further investigation. TRAIL or agonistic TRAIL DR4 and DR5 mAbs are being used clinically; thus, these observations may provide a rational for their incorporation as adjuvants in CD19 CAR CTL-based clinical settings.

Next, we established an *in vitro* model of CD19 CAR CTL-resistant NHL B-sublines (R-NHL) by serial exposure of sensitive parental lines to excessive numbers of CD19 CAR CTLs for an extended period. To obtain a homogenous population, we further performed limiting dilution analysis [38]. We then characterized these resistant sublines: Dual immunostaining showed that surface expression of B cell markers (CD19 and CD20) in R-NHL B-cells remained at levels comparable to those of their parental counterparts. Cytotoxic T-Cells secrete large quantities of type I cytokines (e.g., IFN-γ) upon specific recognition of tumor targets. The results of recognition assays showed comparable levels of IFN-γ secretion by CD19 CAR CTLs upon recognition of both sensitive (parental) and R-NHL B-sublines implying that the recognition compartment (CD19) on R-NHL B-cells remains unmodified during the process of acquisition of resistance. Yet, despite efficient recognition, R-NHL sublines developed resistance to CD19 CAR CTLs as well as cross-resistance to CD19 CAR Jurkat (sorted to 100% purity), activated Jurkat (human T-Cells line), and lymphokine-activated killer (LAK) cells. These observations imply that the development of resistance is independent of down-regulation or loss of CD19 on NHL B-cells and might be due to intrinsic factors such as aberrant apoptotic machinery [38].

Lastly, we attempted to design an innovative approach to overcome acquired resistance of NHL B-cells to CD19 CAR CTLs [38]. We speculated that abnormal levels of apoptotic-related proteins might be responsible for resistance. Initiation or cessation of extrinsic and intrinsic apoptotic signaling pathways depends on the balance between the expression of pro- and anti-apoptotic proteins. Decrease in pro-apoptotic such as Bax, BAD, Bid, Bak and increase in anti-apoptotic such as $Bcl\text{-}_{xL}$, Bcl-2, Mcl-1, survivin, and Bfl-1 protein levels is frequently noticed among various cancers [39,40]. For instance, the Bcl-2 inhibitor ABT-737, a small molecule BH3 mimetic, effectively kills ALL blasts by disrupting the Bcl-2/Bax complex [41]. Another BH3 mimetic, Navitoclax, has significant success against CLL [42].

Our preliminary data implied that R-NHL B-cells have deregulated apoptotic machinery [38]. Although these results require further investigation, they suggest that restoration of expression levels of apoptotic regulators to skew towards a proapoptotic intracellular milieu can sensitize R-NHL B-cells to CD19 CAR CTLs. Multiple strategies are employed to supersede the resistant mechanisms of R-NHL B-cells, including the use of FDA-approved drugs with known anti-tumor properties including histone deacetylase inhibitors (HDACis) and Celecoxib. Subtoxic and clinically achievable concentrations of these drugs have the ability to regulate the expression pattern of apoptotic genes rendering tumors more sensitive to apoptosis and bypass immune-resistance [19, 43-48]. Thus, we examined if Celecoxib and HDACi pretreatment of R-NHL B-cells can sensitize them to apoptotic stimuli delivered by CD19 CAR CTLs. We showed that short-term treatment of R-NHL B-cells to clinically achievable and non-toxic doses of HDACis (SAHA, LBH589), and Celecoxib mostly reversed their resistance to CD19 CAR CTL [38]. These results suggest that chromatin remodeling drugs and the anti-inflammatory drug Celecoxib (Celebrex) can partially sensitize R-NHL B-cells to CD19 CAR CTL- and rhTRAIL-mediated apoptosis. These FDA-approved drugs can be safely used in clinical settings of NHL therapy. The *in vitro* results presented in this study, while obviously require further preclinical examination, may provide rational biological/ molecular basis for incorporation of FDA-approved small molecule immune sensitizers in CD19 CAR CTL-based clinical treatment protocols of NHL patients [38].

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This work is dedicated to the loving memory of Mori Forouzandeh.

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