Leveraging chemotherapy-induced lymphopenia to potentiate cancer immunotherapy

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First-line chemotherapy to combat primary malignant brain cancer is often accompanied by lymphopenic immunologic deficiency. Although counterintuitive, chemotherapy-induced lymphopenia can provide excellent host conditioning that may actually be leveraged to potentiate antitumor immunotherapy. We discuss here our preclinical and clinical experiences applying immunotherapy against glioblastoma, the most common and lethal primary malignant brain tumor, as well as the use of immunotherapeutics in the setting of standard-of-care temozolomide chemotherapy.

Chemotherapy is standard-of-care (SOC) treatment for patients with most types of aggressive and advanced-stage cancers. The agent of choice for the treatment of glioblastoma (GBM), the most common and most lethal primary malignant brain tumor, is temozolomide (TMZ). TMZ is an oral alkylating agent that inactivates the DNA repair enzyme O6-methylguanine-DNA methyltransferase. In a recent Phase III randomized study for newly diagnosed GBM, TMZ combined with external beam irradiation prolonged median survival up to 15 months.1 GBM, however, remains uniformly lethal, creating a desperate need for novel therapies that can be implemented safely alongside current SOC treatments.

To this end, immunotherapy has emerged as a leading strategy targeting malignant disease, especially for resident brain tumors. This approach aims to elicit cancer cell-specific cellular and humoral responses that recognize and eliminate neoplastic cells with exquisite precision. Although immune-retargeting can be accomplished in a number of ways, vaccination and adoptive cell therapy (ACT) represent 2 of the most promising techniques currently being explored in patient trials. The earliest attempts to translate these strategies into the clinic were met with a great deal of skepticism and produced largely unimpressive results. One of the hurdles to achieving ideal efficacy has been the a priori assumption that the implementation of optimal immunotherapy requires an intact immune system—a line of reasoning which has largely precluded patients with GBM due to the immune-compromising side-effects of SOC chemotherapy.

Our increasing knowledge of immune reconstitution following chemotherapy-induced lymphopenia has recently yielded critical information challenging this view. A wealth of evidence has now demonstrated that lymphopenia transiently leads to a reduction of endogenous lymphocytes, which creates a host environment with homeostatic elevations in several cytokines. These critical mediators, such as interleukin (IL) -2, IL-7, IL-15, and B lymphocyte stimulator (BLyS), provide positive signals that potentiate the functionality and clonal expansion of T and B cells, which in turn support reconstitution of the adaptive immune system.2-4 Key signals aimed at restoring the leukocyte compartment also lead to an abundance of antigen presenting cells (APCs), and can trigger critical immunostimulatory pathways via Pattern Recognition Receptors (PRRs) that result in the activation of dendritic cells (DCs), which are professional APCs, as well as the induction of a subset of cytokines, such as IL-12 and type I interferons, which are known to promote strong cellular and humoral responses.5 Lymphodepletion not only precipitates this surge in the availability of homeostatic cytokines, but may also eliminate regulatory cell subsets, which have been shown to directly limit or prevent the antitumor activity of tumor-reactive lymphocytes.4

Remarkably, the processes underlying immune reconstitution can be readily leveraged with immunotherapy to potentiate antitumor responses (Fig. 1). Our experience with TMZ has demonstrated this proof-of-principle for both the...
Administration of TMZ depletes host T cells, increases levels of circulating pro-inflammatory cytokines, and reduces regulatory T-cell counts. In preclinical studies, we have shown that this environment synergizes with immunotherapy by increasing the frequency of adoptively transferred tumor-specific T cells, significantly prolonging the median survival of mice with established tumors in the brain. Interestingly, this effect was dose-dependent, with enhanced efficacy observed at the highest doses of TMZ, presumably due to a greater degree of host lymphodepletion. Importantly, our clinical data consistently recapitulate this phenomenon, as demonstrated by a Phase II study in which patients with GBM treated with high dose TMZ showed elevated levels of BLyS that was, in turn, associated with an increase in antigen-specific titers in patients undergoing B cell specific vaccination against the variant III tumor-specific mutation of the epidermal growth factor receptor (EGFRvIII).

Furthermore, patients conditioned with a higher degree of TMZ-induced lymphopenia displayed a significant increase in progression-free and overall survival, exciting findings which have subsequently led to the initiation of an ongoing Phase III international multicenter study (NCT01480479).

Indeed, there is now considerable evidence to support the finding that lymphopenia—a previously undesired consequence of chemotherapy—may actually synergize, rather than hinder, antitumor immunotherapeutic strategies (Fig. 1). This interplay is being explored for patients with several cancer types, including non-small cell lung cancer (NSCLC) and melanoma. In a recent Phase IIb study, patients with NSCLC treated with an experimental vaccine targeting mucin-1 (MUC-1) achieved significantly prolonged progression-free survival in the setting of first-line cisplatin and gemcitabine chemotherapy—results that have propelled ongoing Phase III multicenter studies (NCT01383148). In a separate Phase I/II study of patients with melanoma, first-line chemotherapy dacarbazine has been shown to enhance T-cell responses in patients undergoing peptide vaccination. While this vaccine regimen is currently being evaluated in the context of SOC chemotherapy, other immunotherapies are being coupled with experimental chemotherapeutic regimens in the adjuvant setting. Several of these agents, such as cyclophosphamide, paclitaxel, doxorubicin, and 5-fluorouracil, have demonstrated immunomodulatory properties in early Phase I/II studies that have enhanced responses and improved outcomes in patients undergoing vaccination or ACT. Moreover, host conditioning with high-dose chemotherapy fludarabine and cyclophosphamide has been routinely employed in Phase I/II melanoma trials that evaluate the safety and efficacy of adoptively transferred ex vivo cultured T cells. These studies have been largely based on pioneering work by Rosenberg and colleagues, who have shown that prior lymphodepletive host conditioning may result in prolonged persistence of clonal adoptively-transferred, tumor-reactive lymphocytes, which, in theory, ultimately traffic to tumors and mediate regression. Adoptive transfer of tumor-directed T cells has since been extended to a myriad of blood-borne and solid tumors in this context, lending greater credence to its claim as a global principle.

As immunotherapy continues to grow in relevance for clinical use, what was once believed to be detrimental to the efficacy of this strategy may prove not only to be beneficial, but rather optimal for the elicitation of both cellular and humoral responses. We believe that this synergy will allow clinicians to exploit SOC-induced lymphopenia for an enhanced immunotherapeutic approach to eradicate malignant disease.

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Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.
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