IN THE SPOTLIGHT

Checkpoint Blockade + Chemotherapy: The Right Combination for AML?

Spencer C. Wei[1], James J. Mancuso[2], Naval Daver[3], and James P. Allison[2,4]

Summary: An emerging strategy to enhance the efficacy of immune checkpoint blockade in relapsed/refractory cancers is increasing immunogenic cell death via combination with cytotoxic therapies. Understanding the effects of cytotoxic and immunotherapeutic agents on immune cell populations will enable improved mechanism-based design of combination therapies to maximum efficacy and minimum toxicity.

See related article by Zeidner et al., p. 616 (1).

BACKGROUND

In this issue, Zeidner and colleagues (1) report encouraging results from an open-label phase II clinical study of anti–PD-1 sequenced after high-dose cytarabine (HiDAC) in relapsed/refractory acute myeloid leukemia (R/R AML). Previous attempts to apply chimeric antigen receptor T cells, bispecific antibodies, and innate immune system–based approaches to AML have yielded varying degrees of success (2). Immune checkpoint blockade antibodies when administered as monotherapies have provided limited efficacy against R/R AML with the exception of CTLA-4 inhibition in post-transplant relapsed AML in a small cohort of patients. This study suggests that combination of cytotoxic chemotherapy with immune checkpoint inhibition showed encouraging activity in a population of patients with R/R AML with dismal outcomes, even with approved cytotoxic or targeted therapies [complete remission (CR)/CR with incomplete hematologic recovery rates: 10%–30%; median overall survival (mOS): 4–10 months; ref. 3]. The regimen used showed improved mOS compared with a historical cohort (11.1 months vs. 6.3 months for salvage HiDAC; ref. 4). There were no long-term remissions, but a significant number of patients achieved composite CR (CRc = 46%, minimal residual disease negative = 23%). While the nonrandomized nature of this study makes it difficult to evaluate the efficacy of this treatment versus current salvage chemotherapy regimens, cytotoxic chemotherapy plus immune checkpoint blockade may have a potential

role in treating R/R AML. The authors performed genomic and immunologic characterization examining biological correlates of response. These observations are indicative of enhancement of endogenous antitumor immune responses consistent with known mechanisms of action; more importantly, they highlight biological variables that may possibly be leveraged to induce more effective responses.

Potential rate-limiting steps and broad mechanisms of action of checkpoint blockade have been discussed in depth elsewhere (5). The complexity of the tumor immune response offers many possibilities for improving the response to immunotherapy through combination treatments. For example, combination of hypomethylating agents that boost the immune response by increasing IFNγ production with programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) blockade appeared to provide modest survival benefit to a population of patients with R/R AML, with pretherapy CD3 and CD8 and hypomethylation-naïve status identified as predictors of response (6). The combination of a cytotoxic chemotherapy agent, such as HiDAC, as administered in the current study, should increase tumor cell death and increase antigen display, in turn leading to increased T-cell activation prior to initiation of immune checkpoint inhibition. Here we focus specifically on biological responses and approaches that are informed by the observations reported by Zeidner and colleagues (1). These include modulation of TCF1+ stem-like CD8 T cells, tumor cell immunogenicity induced by chemotherapy (i.e., how to choose which chemotherapy to combine with checkpoint blockade), sequencing of therapeutics, engagement of CD8 versus CD4 T-cell responses, durability of response, and utilization of tumor-intrinsic properties (e.g., tumor driver mutations) to inform therapeutic sensitivity (Fig. 1).

RATIONAL DESIGN OF COMBINATION THERAPY REGIMEN

The goal of combination cytotoxic therapy with immune checkpoint blockade is to maximize immunogenic cell death and minimize the death of immune cells involved in the antitumor response, leading to an enhanced shift in the tumor–immune equilibrium (7). There are several primary

[1]Spotlight Therapeutics, Hayward, California. [2]Department of Immunology, The University of Texas MD Anderson Cancer Center, Houston, Texas. [3]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, Texas. [4]Parker Institute for Cancer Immunotherapy, The University of Texas MD Anderson Cancer Center, Houston, Texas.

Corresponding Authors: Spencer C. Wei, Spotlight Therapeutics, 3953 Point Eden Way, Hayward, CA 94545. E-mail: spencer.wei@spotlighttx.com; and James P. Allison, Department of Immunology, The University of Texas MD Anderson Cancer Center, 7455 Fannin Street, 1SCR3.1035, Houston, TX 77030. Phone: 713-794-1104; E-mail: jallison@mdanderson.org
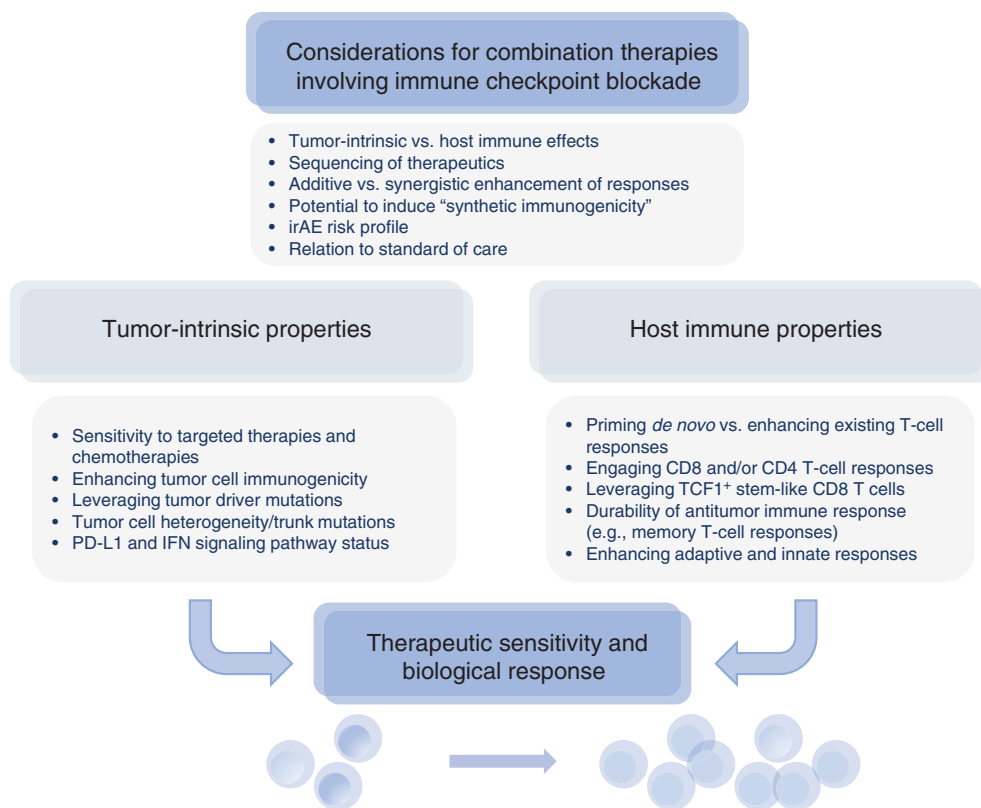
Figure 1. Considerations for rational design of combination therapies involving immune checkpoint blockade. irAE, immune-related adverse event.

factors to be considered for design of combination therapies that include consideration of additive versus synergistic drug interactions (both can be favorable, depending on the context), choice of immune checkpoint blockade therapy, the possibility of synthetic effects from the combination (both in terms of efficacy and adverse events), likely tolerability, and drug sequencing that is compatible with favorable mechanisms of action. In this trial, HiDAC was chosen as the single chemotherapy agent to combine with anti–PD-1 rather than a multiagent regimen to minimize lymphocyte depletion. In addition, combination immunotherapies, especially when combining multiple therapies directly targeting T cells, has increased risk for potential immune-related adverse events. The combination of cytotoxic chemotherapy and immune checkpoint blockade would appear to reduce that risk. Differential effects of various chemotherapy regimens on the immune populations present, if determined in a systematic manner, could inform optimal combinations of cytotoxic chemotherapy with checkpoint inhibitors to maximize tumor cell death and leave the immune cells in the tumor microenvironment receptive to specific checkpoint blockade. On the basis of what is known, it is likely that this combination could be additive in terms of efficacy, although it remains a possibility that synergistic effects could arise from enhanced T-cell priming and initiation of a cascade response. Proper sequencing of the therapies is key to allowing for the greatest potential effect. Notably, the immune checkpoint blockade was started 2 weeks after chemotherapy,

when inflammation is likely to be increased with sufficient time to allow for antigen release and T-cell priming to have occurred. Because PD-1 is inducible and present only on fully activated T cells, this sequencing is also rational based on the mechanism of the drug. A caveat of this approach, however, is that there may already be an immune response (e.g., with activated T cells expressing PD-1) given that patients with R/R AML have already received prior therapies and have variable immune states. Given the relatively modest differences in baseline and on-therapy immune profiles observed in this study (albeit with a small sample size), it should be considered whether concurrent combination therapy could be an alternative effective option.

UTILITY OF HIGH-DIMENSIONAL/ UNSUPERVISED ANALYSIS OF IMMUNE CELL POPULATIONS

High-dimensional approaches have been increasingly utilized to interrogate immune responses and perturbations to cell states. Here the authors utilize dimension reduction and clustering approaches to identify changes in the immune profile in bone marrow, the AML tumor microenvironment, and peripheral blood combined with genomic analyses. Such approaches can be helpful in uncovering latent information, identifying noncanonical cell populations, and parsing the heterogeneity of the immune system. Although limited by sample size and depth of dimensions, the observations

provide clues toward which patients are likely to respond to checkpoint therapy and the mechanisms through which nonresponsive cancers avoid rejection after immunotherapy. Immune profiling revealed a significant increase in regulatory T cells in the blood/bone marrow of nonresponding patients. This potential mechanism by which AML could avoid immune rejection warrants additional study and could potentially yield an avenue to extend efficacy to nonresponding patients.

Often though, observations from high-dimensional profiling provide more questions than answers. For example, an outstanding question in the field is how to leverage TCF1+ stem-like CD8 T-cell populations that mediate a proliferative expansion following anti–PD-1 therapy (8). Consistent with this mechanism, the authors observe here that patients that achieved CRc had higher frequencies of TCF1-expressing CD8 T cells in the bone marrow prior to therapy. The authors define this population as "progenitor exhausted T cells"; however, it remains to be determined whether this population is functionally similar to the stem-like CD8 T-cell population, which has been reported in secondary lymphoid organs (8). If the presence of this population could be used as a biomarker, that could be beneficial; however, this effect is highly variable (driven primarily by two patients with high frequency) with most patients achieving CR having similar levels of this population as patients that did not respond—severely limiting the utility of this population as a biomarker unless confirmed in additional studies. Alternatively, identification of chemotherapeutic regimens that do not affect the TCF1+ CD8 T-cell population could be useful in selection of optimal combination approaches.

ENGAGEMENT OF CD8 VERSUS CD4 T-CELL RESPONSES

Antitumor immune responses can be enhanced in very distinct ways. These include increasing the magnitude of existing cellular responses (adaptive and/or innate), removing suppressive aspects of the tumor microenvironment, shifting the tumor–immune equilibrium (e.g., a chemotherapy that does not affect the immune responses but kills 90% of the tumor), priming new immune responses (e.g., new T-cell clonotypes, distinct cell types), and even generating entirely new populations of effector T cells specific for the tumor (9). Here the authors profiled T-cell populations found in responders and nonresponders, which revealed modulation of CD8 T cells only and not modulation of CD4 T-cell populations. This finding is consistent with the known mechanism of action of PD-1 inhibitors, which modulate the activity of PD-1+ CD8 T cells. It is critical to distinguish that while PD-1 blockade does not modulate CD4 subsets, CD4 T-cell help is critical for response to PD-1 blockade. Together, these observations leave open the possibility that improved efficacy and more durable responses could be achieved through addition of a therapy that modulates CD4 T-cell populations to provide CD4 T-cell help. Given that HiDAC increases antigen presentation, incorporating anti–CTLA-4 could increase efficacy by enhancing the initial T-cell priming responses. As we increasingly understand the underlying biology, combination therapies can be constructed to modulate key responses and rate-limiting steps in tumor immune responses.

LEVERAGING TUMOR CELL–INTRINSIC PROPERTIES

Tumor driver mutations can affect the immune response and responses to immunotherapies. Understanding these relationships could be potentially helpful in enabling patient stratification. Zeidner and colleagues (1) note potential associations between response and tumor mutations. For example, the authors note that none of the four patients with WT1 mutations had a response to treatment, while the three patients without a detectable mutational driver achieved CR. Although these observations are limited by the small number of patients and small number of somatic mutations in AML compared with many solid tumors, they raise the possibility of differential responses based on tumor-intrinsic properties and highlight the issue of how tumor characteristics might be used to guide precision medicine approaches.

Most approaches have focused on identifying driver mutations that are immunosuppressive (e.g., mutations that are associated with increasing PD-L1 expression, although notably, there are many other mechanisms). For example, tumor cell–intrinsic β-catenin signaling can lead to immunosuppression and T-cell exclusion (10). An additional intriguing possibility is that specific driver mutations confer vulnerabilities to specific chemotherapies (or other therapies) that lead to enhanced immunogenicity. Conceptually, this is very similar to synthetic lethality, but here the outcome is immunogenicity rather than tumor cell death. This "synthetic immunogenicity" may be a potential area for investigation to inform combination therapies. Prior studies have identified mechanisms by which tumors can become more immunogenic but have not generally focused on the relationships and systematic characterization of functional outcomes in the context of specific therapies. Utilizing tumor cell–intrinsic properties to identify sensitivity to therapies can be hampered by tumor heterogeneity and clonal diversity. Identification of trunk driver mutations can mitigate this risk. In the context of synthetic immunogenicity, the goal would be to induce enhanced antigen release (by the fraction of sensitive tumor cells), which would then prime immune responses to a broad repertoire of tumor antigens. In this model, chemotherapies that are relatively ineffective at tumor reduction/eradication as single agents could lead to significant effects in the context of combination immunotherapy (e.g., immunogenic cell death of a small fraction of tumor cells would be preferred to nonimmunogenic killing of a large fraction of tumor cells despite benefits of initial tumor reduction).

CONCLUSIONS

The results of this trial demonstrate the potential of rationally designed combinations of cytotoxic chemotherapy with immune checkpoint blockade to treat historically refractory malignancies including R/R AML. While the combination appears to provide benefit (shifts survival curve right on historical comparison), we still need to induce long-term durable responses similar to those observed in other indications to bring checkpoint therapy to the forefront in AML. The immune and mutational profiling performed provides

a potential avenue for iterative improvement of combination therapy for AML. On the most simplistic level, this could be selection of a cytotoxic regimen that specifically results in improved maintenance of effector T cells or upregulation of PD-1^{+} or PD-1^{+} TCF1^{+} CD8 T cells to be paired with PD-1 inhibition. Regardless, further immune profiling of the effects of cytotoxic therapies prior to or concurrent with the addition of checkpoint blockade will be important for improving combination immunotherapy for AML and other difficult malignancies.

Authors' Disclosures

Acknowledgments

REFERENCES

1. Zeidner JF, Vincent BG, Ivanova A, Moore D, McKinnon KP, Wilkinson AD, et al. Phase II trial of pembrolizumab after high-dose cytarabine in relapsed/refractory acute myeloid leukemia. Blood Cancer Discov 2021;2:616–29.
2. Daver N, Alotaibi AS, Bucklein V, Subklewe M. T-cell-based immunotherapy of acute myeloid leukemia: current concepts and future developments. Leukemia 2021;35:1843–63.
3. Short NJ, Rafei H, Daver N, Hwang H, Ning J, Jorgensen JL, et al. Prognostic impact of complete remission with MRD negativity in patients with relapsed or refractory AML. Blood Adv 2020;4:6117–26.
4. Ravandi F, Pierce S, Garcia-Manero G, Kadia T, Jabbour E, Borthakur G, et al. Salvage therapy outcomes in a historical cohort of patients with relapsed or refractory acute myeloid leukemia. Clin Lymphoma Myeloma Leuk 2020;20:e871–e82.
5. Wei SC, Duffy CR, Allison JP. Fundamental mechanisms of immune checkpoint blockade therapy. Cancer Discov 2018;8:1069–86.
6. Daver NG, Garcia-Manero G, Konopleva MY, Alfayez M, Pemmaraju N, Kadia TM, et al. Azacitidine (AZA) with nivolumab (Nivo), and AZA with nivo + ipilimumab (Ipi) in relapsed/refractory acute myeloid leukemia: a non-randomized, prospective, phase 2 study. Blood 2019;134:830.
7. Dunn GP, Old LJ, Schreiber RD. The immunobiology of cancer immunosurveillance and immunoediting. Immunity 2004;21:137–48.
8. Im SJ, Hashimoto M, Gerner MY, Lee J, Kissick HT, Burger MC, et al. Defining CD8+ T cells that provide the proliferative burst after PD-1 therapy. Nature 2016;537:417–21.
9. Wei SC, Anang NAS, Sharma R, Andrews MC, Reuben A, Levine JH, et al. Combination anti-CTLA-4 plus anti-PD-1 checkpoint blockade utilizes cellular mechanisms partially distinct from monotherapies. Proc Natl Acad Sci U S A 2019;116:22699–709.
10. Spranger S, Bao R, Gajewski TF. Melanoma-intrinsic beta-catenin signalling prevents anti-tumour immunity. Nature 2015;523:231–5.