Harnessing Immune Responses in the Tumor Microenvironment: All Signals Needed

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An agonist CD40 monoclonal antibody (CP-870,893), in combination with gemcitabine, is well tolerated in patients with advanced pancreatic adenocarcinoma. The combination results in induction of cytokines, B cell activation, and clinical responses. These findings support testing of immunotherapies in combination with other established and targeted therapies. Clin Cancer Res; 19(22): 6061–3. ©2013 AACR.

In this issue of Clinical Cancer Research, Beatty and colleagues report their findings from a phase I study of an agonist CD40 monoclonal antibody (CP-870,893), given in combination with gemcitabine to 22 patients with previously untreated advanced pancreatic ductal adenocarcinoma (PDA; ref. 1). Most patients experienced transient cytokine release syndrome and showed an induction of systemically released inflammatory cytokines [interleukin (IL)-6, IL-8, IL-10], an increase in costimulatory molecules on B cells (HLA-DR, CD86), and a transient depletion of B cells. The radiographic partial response rate (19%) and median overall survival (8.4 months) were higher than expected for single-agent gemcitabine (9.4% and 6.8 months, respectively; ref. 2), providing encouraging preliminary evidence of clinical activity.

PDA remains one of the deadliest cancers, with the incidence nearly approximating the death rate, and novel therapies are desperately needed. Although immunotherapy is promising for a number of solid tumors, this promise has yet to be realized for PDA. Single-agent therapy using blocking antibodies against negative regulatory pathways, including ipilimumab (anti-CTLA antigen-4, CTLA-4; ref. 3) and BMS-936559 (anti–programmed death ligand-1, PD-L1; ref. 4), has yielded little activity in patients with PDA. Preclinical studies suggest that combination strategies with traditional therapies including chemotherapy and radiation, when given to modify the tumor microenvironment (TME) and release tumor antigens, or with other immunotherapies including vaccines that activate T cells and other immune checkpoint antagonists that block more than one inhibitory signal within the TME at the same time, will likely be required to effectively treat PDA (5).

CD40, a member of the TNF receptor superfamily, is present on antigen-presenting cells (APC), including dendritic cells, B cells, macrophages, and nonhematopoietic (endothelial and some tumor) cells. CD40 stimulation enhances T-cell–dependent antitumor immunity by enhancing the capacity of APCs to prime and activate tumor-specific T cells and T-cell–independent immunity by activating tumoricidal tumor-associated macrophages (ref. 6; Fig. 1). The design of this study was driven by the same group’s preclinical data establishing the collaborative interactions of gemcitabine chemotherapy with CD40 agonist therapy. Although it may seem counterintuitive to use potentially immunosuppressive chemotherapy with immunotherapeutic agents, the enhanced clinical activity of the combination may be the result of the agonist antibody’s activation of the non–T-cell-dependent and/or T-cell–dependent immune responses that are further enhanced by the role of the chemotherapy as a tumor-lytic agent simulating an in situ vaccine by assisting tumor antigen release in the context of CD40 antibody–mediated costimulation of the tumor-residing APCs. Clinically, full dose carboplatin and paclitaxel has also been combined with CP-870,893 for the treatment of advanced solid tumors (7). In addition, ipilimumab has been given with dacarbazine for the treatment of melanoma (8), and with carboplatin and paclitaxel for the treatment of non–small cell lung cancer (9), all without causing detrimental effects to the activity of the immunotherapy. Interestingly, in the lung cancer study, the therapy was most efficacious when the immunotherapy was started during the third cycle of chemotherapy as opposed to being started concurrently, suggesting that sequencing plays an important role mechanistically.

Prior publications by this same group emphasized the important role of tumor-associated macrophages in the antitumor effects of CD40-based therapy (6). Resected specimens from two patients on this clinical study showed a predominance of macrophages and not lymphocytes. Although this finding is interesting, these specimens were obtained several months after the start of therapy and represent a single time point within the TME. Although always a challenge in clinical trials, repetitive biopsies of regressing tumors would provide the best opportunity to accurately elucidate the mechanism of action of CD40-based therapy. In this case, as in other diseases, macrophages...
may be "scavengers" after the response to therapy rather than the mediators of anti-CD40–based therapy. The authors did address this further in an earlier publication using spontaneous tumors in the KPC model, a genetically engineered PDA mouse model, and found that tumor regressions required macrophages and not T cells or gemcitabine (6). This latter finding does bring into question the role of gemcitabine in this combination. F4/80 \( ^+ \) tumor-associated macrophages express CD40. The CD40 antibody engages CD40 on peripheral blood macrophages that then infiltrate the TME. MHC class II and the costimulatory molecule CD86 are upregulated on these macrophages. Macrophage depletion studies suggested that CD40 therapy required macrophages for stromal depletion and antitumor activity. The emphasis on the role of macrophages also underscores the importance of the effects of CD40-based treatment on the stroma. CP-870,893 is thought to bind to peripheral blood monocytes, which then infiltrate the tumor and promote degradation of the stroma. Interestingly, \([18F]\)-fluorodeoxyglucose–positron emission tomography/computed tomography (FDG-PET) responses were more consistently found in the primary tumor (6 of 8 patients) with more heterogeneous responses in the metastatic lesion. Improved overall survival correlated with a decrease in FDG uptake in the hepatic lesions. Primary pancreatic tumors more often have a dense desmoplastic reaction in comparison with metastatic lesions (ref. 10; C. Iacobuzio-Donahue, Johns Hopkins Medical Institutions, personal communication). This difference in the stromal contribution to the tumor mass in the primary tumor versus metastases might explain the more consistent FDG responses observed in the primary tumors in this study.

On the contrary, prior work in a transplantable KPC tumor model showed that T cells and gemcitabine were required to achieve tumor regressions (11). Perhaps the spontaneous tumor model is more biologically relevant and the role of T cells should be minimized. Alternatively, the need for gemcitabine and T cells in the transplantable model might suggest that a "vaccine" consisting of gemcitabine and tumor cells is most effective when administered peripherally and not as in situ release in the inhibitory TME. T cells are necessary for immune memory and induction of durable responses.

CD40-based therapy is unique in that the antibody is agonistic and provides costimulatory effects as opposed to the antagonistic approach of anti-CTLA-4 and anti-PD-1/anti-PD-L1 therapies that block negative signals. Unlike these other agents, CD40 therapy is showing preliminary efficacy without the immune-related autoimmune-like toxicities. Additional studies should focus on understanding both the mechanism and the contribution of the individual components to the therapeutic effect. Gemcitabine does have single-agent activity in patients with PDA, and preclinical data suggest that CP-870,893 has single-agent activity. As the authors point out, this is a small study with large confidence intervals. Future studies would also need to address how the agent would be developed within the rapidly changing treatment landscape of PDA.
chemotherapy using FOLFIRINOX (oxaliplatin, irinotecan, leucovorin, and 5-fluorouracil) in patients with good performance status resulted in a median overall survival of 11.1 months (2). Gemcitabine and nab-paclitaxel has recently received U.S. Food and Drug Administration approval for metastatic PDA given a median overall survival of 8.5 months (12). If results from this current study were reproduced in a larger study in which the combination were randomized against one of these standard therapies, this less toxic therapy would be comparable and possibly preferable to the current standards. Combinations with other immunotherapies may be another possibility. The authors suggest the possibility of combining CP-870,893 with these newer chemotherapy regimens. Although immunosuppression remains a concern, these treatments have a higher response rate, which would lead to better antigen release and stromal breakdown. Given signs of clinical activity and the myriad of downstream stimulatory effects, CD40 is an attractive target for further development for the treatment of PDA.

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No potential conflicts of interest were disclosed.

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