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Translational Immunotherapeutics: Chemoimmunotherapy for Malignant Pleural Mesothelioma

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Despite its rarity and poor prognosis, malignant pleural mesothelioma (MPM) has generated significant interest, likely due to its association with asbestos exposure and the hypothesis that it originates from a chronic inflammatory state within the pleura. In an effort to clear asbestos fibers, macrophages make repeated failed attempts at phagocytosis, resulting in continued generation of reactive oxygen species with subsequent production of inflammatory cytokines and increased recruitment of immune cells.[1] This process, often referred to as ‘‘frustrated phagocytosis,’’ represents a chronic inflammatory state that results in malignant transformation of mesothelial cells. Currently, even with trimodality therapy (chemotherapy, surgical resection, and hemithoracic radiation), the median survival for patients with epitheloid MPM, the most common type of MPM, is only 17 months. For MPM patients presenting with unresectable disease, the combination of pemetrexed and cisplatin is the most effective therapy, although it achieves a median survival of only 12 months.[2] Responses to second- and third-line treatment are rare in patients for whom chemotherapy has failed.

Despite the aggressive biological nature of MPM, clinical and preclinical investigations have correlated antitumor immune responses with improved survival in MPM patients,[3] which is similar to what has been observed in patients with other solid tumors (melanoma and ovarian cancer). In a cohort of 175 patients with epitheloid MPM, we found that patients with high chronic stromal inflammatory responses had better median overall survival than those with low chronic inflammatory responses.[4] Importantly, on multivariate analysis, chronic stromal inflammation remained an independent predictor of survival. Furthermore, we and others have demonstrated that tumor infiltration of CD8+ T lymphocytes is an independent prognostic factor for MPM patients.[5–7] The efforts to promote immune responses have led to the investigation of immunotherapeutic strategies targeting cancer-associated antigens by use of monoclonal antibodies, recombinant immunotoxins, vaccines, and genetically engineered T-cells. Targeted antigens can be either cell-surface antigens, such as mesothelin (MSLN), or intracellular antigens, such as WT-1. Because of their ease of targeting, cell-surface antigens are favored for immunotherapeutic approaches.

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An ideal cancer-associated antigen to target by immunotherapeutic approaches (1) is not expressed or is expressed at relatively lower levels in normal tissues, compared with cancer cells, (2) is expressed in a majority of cancer patients, and (3) plays a role in promoting cancer aggressiveness. MSLN, one such cancer-associated antigen originally described by Ira Pastan,[8,9] being investigated in MPM patients, is expressed at very low levels in normal mesothelial cells lining the pleura, peritoneum, and pericardium. MSLN is overexpressed in epitheloid mesotheliomas[10] and in other solid cancers, including ovarian, pancreatic, lung, stomach, and esophageal cancer, cholangiocarcinoma, and triple-negative breast cancer.[11–13] The *MSLN* gene encodes a 71-kDa precursor protein that is processed into megakaryocytic potentiating factor (MPF) that is secreted from the cell into the blood, and MSLN that is bound to the cell membrane by phosphatidyl inositol but is slowly shed from the cell surface via the action of TNF-α converting enzyme. MSLN has been shown to bind to MUC16 (CA125), and this interaction has been implicated in the intracavitary spread of ovarian cancer.[14] Our group has demonstrated—both in an orthotopic MPM mouse model and in patients—that MSLN overexpression is correlated with locoregional invasion characteristics of MPM.[10] MSLN overexpression is associated with expression of metalloproteinase-9 (a protein involved in the degradation of extracellular matrix), which facilitates cancer cell migration and local invasion. Studies of *MSLN* gene knockout (-/-) mice indicate that *MSLN* is not essential for normal development and reproduction,[15] but recent studies have shown that *MSLN* might regulate cancer cell growth.[16] Our group found that MSLN expression was correlated with tumor aggressiveness, as well as decreased overall survival, in a cohort of 1209 early-stage lung adenocarcinoma patients.[12]

Given its high level of expression in cancer and its limited expression in normal tissues, MSLN provides a safe target for tumor-specific therapies. SS1P is a recombinant anti-MSLN immunotoxin that consists of a murine anti-*MSLN* variable antibody fragment (Fv) linked to PE38, a truncated portion of *Pseudomonas* exotoxin A. In a phase I clinical trial of patients with advanced, therapy-resistant *MSLN*-expressing cancer, administration of SS1P, for a total of 3 doses, was well tolerated.[17] Pleuritis was the dose-limiting toxicity. The most commonly reported adverse events were hypoalbuminemia and fatigue. SS1P had limited antitumor activity, the investigators hypothesized that the lack of activity of SS1P could be attributed to the limited tumor penetration, caused by tumor cells density, high interstitial pressure, and lack of functional lymphatics within tumors. In mice with MSLN-expressing human tumor xenografts, SS1P had modest antitumor activity by itself, but when it was combined with chemotherapy, synergy was observed.[18] Investigators led by Drs. Pastan and Hassan demonstrated that, by killing tumor cells, chemotherapy disrupts the close packing of tumor cells, allowing better penetration of immunotoxin into the tumor.

In this issue of *Cancer*, in the first evaluation of SS1P in combination with pemetrexed and cisplatin in chemotherapy-naive MPM patients, Hassan et al. report objective tumor responses that are higher than would be expected with chemotherapy alone, with no overlapping toxicities.[19] The primary objective of this phase I study was to determine the safety and MTD of SS1P in combination with pemetrexed and cisplatin in chemotherapy-naive patients with advanced MPM. The secondary objectives were to assess the tumor radiological response, SS1P pharmacokinetics, and serum biomarkers of response (*MSLN*,

MPF, and CA-125). Although this was a phase I study designed to evaluate the feasibility and safety of combination chemoimmunotherapy, the results of this trial (response rates, 60% in all evaluable patients vs. 77% in patients treated at the MTD) compare favorably with those of the pivotal trial of pemetrexed and cisplatin in MPM (objective response rate, 41% vs. 17% in patients treated with cisplatin alone). In addition, Hassan et al. demonstrate the utility of incorporating the biomarkers of response into an early-phase clinical trial. Although baseline *MSLN*, MPF, and CA-125 levels did not predict the response to SS1P and chemotherapy in this small cohort of patients, the investigators found that changes in *MSLN* and MPF levels were better reflectors of tumor response, compared with changes in CA-125 levels.

Immunotoxins such as SS1P, which combine a bacterial toxin with an antibody, can provoke the patient's immune system by generating antibodies against it, destroys it before it can reach its target and deliver toxin to the tumor. In their publication in *Science Translational Medicine*,[20] Hassan et al. demonstrated a novel approach to overcome this obstacle: treating chemotherapy-resistant MPM patients with pentostatin and cyclophosphamide—chemotherapeutic agents that can deplete lymphocytes and prevent the formation of antibodies after administration of SS1P. This treatment combination delayed formation of antibody, allowing the patients to receive multiple cycles of SS1P and resulting in improved outcomes. Some of the responses demonstrated in these two publications are remarkable for an aggressive malignancy such as MPM.[20] Other methods of preventing antibody response developed by this group include mutating immunodominant epitopes to generate a less immunogenic antibody-toxin conjugate and removing immunotoxin domains that are not necessary for cytolytic function.[21]

Impressive results with MSLN-targeted therapies are not, however, unique to MPM patients. In a phase II trial of pancreatic cancer, a comparably aggressive malignancy, MSLN-targeted vaccine combined with granulocyte macrophage colony-stimulating factor–expressing cells showed promising results, with prolonged survival observed in patients with MSLN-specific immune cell responses.[22] Although MSLN-specific T-cell responses have been shown to be beneficial in pancreatic cancer patients, no such data are available on MPM patients.

Some of these responses are attributed to endogenous immune responses generated to cancer-associated antigens from lysed cancer cells. The development of a broad tumor-specific adaptive immune response, caused by epitope spreading following tumor destruction and inflammation, has been proposed to be an important secondary mechanism underlying the potency of immunotherapy. In a novel approach of targeting MSLN with adoptively transferred MSLN-specific chimeric antigen receptor mRNA–engineered T-cells, investigators from the University of Pennsylvania have demonstrated antibody responses to a number of self-proteins, following chimeric antigen receptor T-cell infusion in patients.[23]

Although chemotherapy has long been considered to be immune-suppressive, recent data indicate that cytotoxic drugs treat cancer, at least in part, by facilitating an immune response to the tumor. Chemotherapy-induced tumor cell lysis can induce an adaptive immune response specific to the tumor. In addition, chemotherapy drugs can promote anti-tumor

immunity through largely unappreciated immunologic effects on both malignant and normal cells present within the tumor microenvironment, including enhanced cytokine and chemokine secretion by the tumoral stroma, enhanced proimmune surface proteins, and altering tumor vasculature. These subtle immunomodulatory effects are dependent on the drug itself, its dose, and its schedule. Preclinical evidence suggests that cisplatin favorably modulates the immune system by upregulating MHC class I expression; by increasing the recruitment, infiltration, and proliferation of various effector cells; by improving the lytic activity of cytotoxic effectors; and by downregulating the immunosuppressive microenvironment.[24] While cisplatin is a widely used chemotherapeutic agent that has been studied for its immunomodulatory effects in solid malignancies, similar tumor immunity reengineering approaches with other chemotherapeutic agents, such as doxorubicin, fludarabine, and oxaliplatin, have been attempted in hematological and solid malignancies. Lymphodepleting agents, as used by Hassan et al. in MPM patients, likely have beneficial immunomodulatory effects aside from their well characterized ability to prevent an immunotoxin antibody response. Lymphodepletion can deplete T regulatory cells and enhance the availability of prosurvival and proliferative homeostatic cytokines to tumor-specific T-cells and NK cells. These advantages have thus far been documented in models of adoptive T-cell therapy. Further studies are needed to document their role in enhancing anti-MSLN immunotoxin therapy.

The recent approval of checkpoint blockade agents heralds a new era in chemoimmunotherapeutic approaches and has led to heightened interest in immunotherapy as a valid approach to cancer treatment. The results of ongoing preclinical studies suggest that rationally combining chemotherapy-induced immune activation with checkpoint blockade agents has synergistic efficacy to maximize the benefits of endogenously generated antigen responses. Radiotherapy is another standard-of-care therapy that has been shown to activate the immune system. A recent phase II clinical trial from the University of Toronto investigated immediate preoperative hemithoracic intensity-modulated radiation therapy followed by extrapleural pneumonectomy in highly selected patients and found a 3-year overall survival of 84%.[25] Although this treatment strategy does not yield better local control than the more conventional approach of surgical resection followed by hemithoracic radiation, it is associated with remarkably good survival, resulting in a speculative hypothesis that preoperative radiation therapy may activate the immune system against cancer—an idea supported by recent preclinical findings that show synergistic efficacy in solid tumors when radiation therapy and immune checkpoint blockade are combined.

With their systematic bench-to-bedside-and-back-to-bench investigative approach, the group at the National Cancer Institute led by Pastan and Hassan has demonstrated an ideal paradigm for translational immunotherapeutics that not only can benefit mesothelioma patients but also holds promise for many other solid cancers. Our improved ability to perform immune monitoring of both the systemic and tumoral microenvironment in conjunction with tumor biomarkers has provided an opportunity to measure antitumor immune responses even in early-phase clinical trials. A detailed understanding of the cellular and molecular bases of the interactions between chemotherapy drugs, radiation therapy and the immune system is essential to be able to devise an optimal strategy for integrating new immune-based therapies into the standard of care for various cancers, and to

ensure the greatest long-term clinical benefit in the treatment of traditionally therapy-resistant cancer patients.

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