An Abscopal Response to Radiation and Ipilimumab in a Patient with Metastatic Non–Small Cell Lung Cancer

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Abstract

A posteriori evidence suggests that radiotherapy to a targeted tumor can elicit an immune-mediated abscopal (ab-scopus, away from the target) effect in nontargeted tumors, when combined with an anti-CTLA-4 monoclonal antibody. Concurrent radiotherapy and CTLA-4 blockade induced immune-mediated abscopal effects in poorly immunogenic preclinical tumor models and patients with metastatic melanoma. However, no such reports exist for patients with metastatic lung adenocarcinoma. We report the first abscopal response in a treatment-refractory lung cancer patient treated with radiotherapy and ipilimumab (a human anti-CTLA-4 monoclonal antibody). A posttreatment increase in tumor-infiltrating cytotoxic lymphocytes, tumor regression, and normalization of tumor markers was observed. One year after treatment with concurrent radiotherapy and ipilimumab, the patient is without evidence of disease. Cancer Immunol Res; 1(6); 365–72. ©2013 AACR.

Introduction

The abscopal (ab-scopus, away from the target) effect is a term used to describe radiotherapy-induced tumor regression in lesions distant from a targeted site, and has been known for six decades as a rare unexplained phenomenon in patients receiving local radiotherapy (1). We hypothesized that the abscopal effect may result from a radiotherapy-induced immunogenic type of cancer cell death capable of generating an in situ vaccine (2–4). In support of this notion, interventions that promote the functionality of dendritic cells or improve T-cell activation are required to produce the abscopal effect (5–8). This strongly suggests that, while radiotherapy alone may be efficient at exposing cryptic tumor antigens, tumor cell–induced immunosuppression and immunotolerance hamper the development of therapeutically effective antitumor immune responses (3, 4).

Immunotherapeutic strategies aimed at overcoming immunotolerance and improving the activation of antitumor T cells represent a new promising therapeutic approach (9). Among them, the human anti-CTL antigen-4 (CTLA-4) antibody, ipilimumab, has demonstrated activity in metastatic melanoma treatment, for which it has U.S. Food and Drug Administration (FDA) approval (10, 11). Yet, the role of ipilimumab in other malignancies and in combination with radiotherapy still remains investigational.

In non–small cell lung cancer (NSCLC), ipilimumab has been tested in combination with chemotherapy [paclitaxel, 175 mg/m2 body surface area (BSA), and carboplatin (area under the curve, 6), infused every 3 weeks] in a phase II trial, including 204 patients with stage IIIB/IV or recurrent disease (12). Induction ipilimumab was administered every 3 weeks for four doses at 10 mg/kg body weight, either concurrently with chemotherapy (concurrent regimen) or after two doses of chemotherapy (phased regimen). Patients without disease progression or adverse effects from ipilimumab continued with maintenance therapy every 12 weeks. The study met its primary endpoint of improved immune-related progression-free survival (referred to as irPFS, which takes into account tumor regression in the presence of new lesions) and the endpoint of PFS for the phased regimen, but not the concurrent regimen, when compared with chemotherapy alone (control regimen; refs. 12, 13).

A difference was observed in the immune-related best overall response rates (irBORR) between the control regimen and the phased regimen, 18% versus 32%. In addition, a difference was observed in the median PFS between the control regimen and the phased regimen, 4.2 months versus 5.1 months. However, no difference was observed in the irBORR between the control regimen and the concurrent regimen, 18% versus 21%. Also, no difference was observed in the median PFS between the control regimen and the concurrent regimen, 4.2 months versus 4.1 months. Of note, on subset analysis, the nonsquamous histology group, including adenocarcinomas, treated with the phased regimen demonstrated a trend toward a worsened hazard ratio (HR) for overall survival, when compared with chemotherapy alone [HR, 1.17 (95% CI, 0.74–1.86)]. Because of these results, patients with squamous cell histology are currently being recruited for a phase III trial comparing the phased regimen with the control regimen for first-line treatment (14).
The improved efficacy of the phased approach, as opposed to the concurrent regimen, suggests that additional factors (other than CTLA-4 blockade) influence tumor-specific T-cell responses in patients with advanced-stage NSCLC. The observed differences may have been the result of the quality of tumor cell death (immunogenic vs. nonimmunogenic) or the immune-modifying effects (inhibitory vs. stimulatory) of chemotherapy at the time of ipilimumab administration (4, 12). These are some of the issues that underscore the challenges that remain in designing optimal combination therapies with ipilimumab.

Interestingly, when given as a monotherapy in patients with NSCLC, CTLA-4 blockade demonstrated no difference in PFS as compared with best supportive care (BSC). In a phase II trial, 87 patients with NSCLC (locally advanced or metastatic) treated with four or more cycles of first-line platinum-based therapy [resulting in either stable disease or response per Response Evaluation Criteria in Solid Tumors (RECIST) criteria] were randomized to tremelimumab (a CTLA-4–blocking immunoglobulin G2 monoclonal antibody) as maintenance therapy (n = 43) or BSC (n = 43; ref. 15). Tremelimumab did not improve PFS; however, 2 (4.8%) partial responses (out of 9 patients without disease progression) were seen in the tremelimumab arm, whereas no partial responses (out of 6 patients without disease progression) were seen in the BSC arm. On the basis of these results as a single agent in NSCLC, future development of tremelimumab has not been pursued (14).

We previously demonstrated in preclinical models of poorly immunogenic carcinomas not responsive to anti-CTLA-4 monotherapy that local radiotherapy synergizes with anti-CTLA-4 antibody. Antitumor T-cell responses that inhibit the growth of locally irradiated tumors as well as their nonirradiated metastatic counterparts were demonstrated (abscopal effect; refs. 5, 8, 16). Consistent with these findings, an abscopal effect was recently reported in 2 patients with treatment-
refractory melanoma receiving radiotherapy with ipilimumab (17, 18). However, until now it was unknown whether radiotherapy can potentiate the response to CTLA-4 blockade in tumor types that have previously shown little to no clinical response. Herein, we report the first case of an abscopal response in a patient diagnosed with metastatic NSCLC treated with radiotherapy and ipilimumab. Remarkably, the patient showed regression, not only at the radiotherapy-targeted site but also in multiple abscopal sites of disease, including visceral and skeletal metastases.

Case Presentation

In March 2010, a 64-year-old Caucasian male with a 70 cigarette-pack-year history presented with a palpable left supraclavicular nodule. An excisional biopsy of the mass showed metastatic adenocarcinoma with an immunohistochemical profile consistent with a lung primary (CK7- and TTF-1–positive and CK20- and CDX2–negative). The patient’s initial positron emission tomography/computed tomography (PET/CT) scan showed two right upper lobe nodules, a left lower lobe nodule, and right supraclavicular and bilateral hilar/mediastinal adenopathy. He was staged as T1bN3M1a (stage IV) according to the American Joint Commission on Cancer seventh edition cancer staging manual, with a predicted median survival of 7 months (19). The patient was initiated on pemetrexed, 500 mg/m² BSA and carboplatin (area under the curve, 5) given every 3 weeks for six cycles. After the sixth cycle, a surveillance PET/CT showed a decrease in size and metabolic activity of both the right supraclavicular adenopathy (from 2.8 cm × 1.7 cm and a standard uptake value (SUV) of 10.2 to 2.0 cm × 1.2 cm and SUV of 3.8) and the left lower lobe nodule (from 6 mm and SUV of 2.3–3 mm and undetectable SUV). The two right upper lobe nodules and hilar/mediastinal nodal disease remained stable in size and metabolic activity.

The patient, thereafter, continued maintenance therapy with pemetrexed, 500 mg/m² BSA alone, given every 3 weeks. However, after three cycles, he developed severe lower extremity cellulitis, at which point the pemetrexed was temporarily discontinued. After antibiotic treatment and resolution of the cellulitis, he received an additional three cycles of pemetrexed and subsequently underwent a repeat PET/CT. The PET/CT revealed stable disease in the right upper lobe and left lower lobe nodules and improvement in the size and metabolic activity in the right supraclavicular and hilar/mediastinal adenopathy.

From February 2011 to April 2011, systemic chemotherapy was interrupted to start radiotherapy to the metabolically active right lung nodules and the right supraclavicular, right hilar, and mediastinal adenopathy to a total dose of 59.4 Gy delivered over 33 fractions. Subsequent chest CTs in May and July 2011, in comparison with the CT before radiotherapy, showed a decrease in size of the irradiated pulmonary nodules and adenopathy. However, in September 2011, a surveillance PET/CT revealed increased metabolic activity and size of the right upper lobe nodule and the previously seen left lower lobe nodule. Treatment with pemetrexed, 500 mg/m² BSA alone was resumed and given every 3 weeks for an additional 10 cycles.

In June 2012, a repeat PET/CT revealed disease progression with new hypermetabolic liver lesions, new periaortic adenopathy, and a new bony lesion in the sacrum. In addition, the right upper lobe and left lower lobe nodules and hilar/mediastinal adenopathy showed an increase in metabolic activity.

Figure 2. Ipilimumab and local radiotherapy result in an abscopal response. PET imaging and select fused PET/CT axial images from August 2012 (left) and January 2013 (right) are displayed. The axial images in the second row reveal the hypermetabolic liver lesion that was targeted and responded to radiotherapy (white arrows, second row). An abscopal response was seen in a left lower lobe lung lesion (white arrows, third row) and a left sacral lesion (white arrows, bottom row). A mixed response was seen in the hilar/mediastinal lymph nodes (striped arrows, third row).
The patient was then treated with gemcitabine, 750 mg/m² BSA, and vinorelbine, 30 mg/m² BSA, given every 2 weeks. After the fourth cycle, in August 2012, a PET/CT showed further disease progression in the liver and growth of new lytic lesions in the bony pelvis, thoracolumbar spine, and right humerus (Figs. 1 and 2).

Figure 3. Treatment timeline and the absolute peripheral blood cell counts. A detailed clinical timeline is displayed (A, top). A PET/CT on June 8, 2012, showed disease progression, prompting a change in the patient’s chemotherapy regimen. On June 15, 2012, the patient was started on a chemotherapy regimen containing gemcitabine and vinorelbine. The green marker indicates the treatment timeline for gemcitabine and vinorelbine (A, top). A repeat PET/CT on August 6, 2012, showed continued disease progression. From August 22, 2012, to August 31, 2012, the patient was treated with concurrent radiotherapy (RT) and ipilimumab. Afterward, he received three additional cycles of ipilimumab alone. The blue marker indicates the treatment timeline for radiotherapy and ipilimumab [A (top) and B], and data plotted to the right of the vertical dashed line in each graph represents postinitiation of radiotherapy and ipilimumab treatment [A (bottom three graphs) and B]. The final dose of ipilimumab was given on October 26, 2012. Imaging on November 8, 2012 (CT of the chest, abdomen, and pelvis) and January 17, 2013 (PET/CT), showed significant treatment responses. During the course of treatment, the patient had serial blood draws. The results of the peripheral absolute blood cell counts (white blood cells [WBC], absolute leukocyte count [ALC], and absolute eosinophil count [AEC]) are displayed as number of cells (×10³) per μL of whole blood (A, bottom three graphs), in accordance with the aforementioned treatment timeline (A, top). A dramatic drop in carcinoembryonic antigen levels (a nonspecific tumor marker) was observed after treatment with radiotherapy and ipilimumab (B). The marker peaked at 119.6 ng/mL (normal levels 0–5 ng/mL) on September 7, 2012, showing a dramatic drop to 5.8 ng/mL on October 26, 2012, and thereafter was maintained at normal levels.
Ipilimumab (received as a compassionate exemption) with local radiotherapy to one of the hepatic metastases was initiated, with the intent to generate an abscopal response. The experimental nature of this approach was extensively discussed with the patient, who was informed of the only two available reports in melanoma and the lack of available evidence for patients with NSCLC.

The patient was simulated in the supine position and his CT/simulation was registered to the August 2012 PET/CT for treatment planning purposes (Fig. 1). The most metabolically active liver mass, located in the caudate lobe, was selected as the radiotherapy target and contoured as the gross tumor volume (GTV). An additional 0.5-cm margin was added to create a clinical target volume (CTV), and another 0.5 cm margin was added to the CTV to create a planning target volume (Fig. 1). Radiotherapy to a total dose of 30 Gy distributed over five fractions was delivered over a period of 10 days with 6-MV photons and a coplanar five-field intensity-modulated technique (Fig. 1). The day after the first radiotherapy fraction, the patient was infused with ipilimumab, 3 mg/kg body weight. Thereafter, the patient completed three more cycles of ipilimumab, 3 mg/kg body weight, infused at 3-week intervals. The patient tolerated radiotherapy and ipilimumab without any treatment-related adverse events. Maintenance infusions of ipilimumab were not given afterward.

Results

After treatment with radiotherapy in combination with ipilimumab, a posttreatment chest CT (November 2012) and PET/CT (January 2013) showed a dramatic treatment response of the patient’s known disease. Not only was an objective response detected in the radiotherapy field, but striking responses were also observed at distant sites (Fig. 2). Metabolic activity seen previously at the irradiated site in the liver resolved. In addition, there was resolution of multiple nonirradiated foci within the liver and skeleton. There was significant decrease in the metabolic activity and size of the left lower lobe nodule and the previously irradiated right upper lobe nodule. However, a mixed metabolic response was seen in the right hilar adenopathy (increased SUV uptake from 4 to 5.4).

After treatment with ipilimumab and radiotherapy, there was an increase in absolute lymphocyte counts (ALC) and absolute eosinophil counts (AEC), two biomarkers associated with improved survival rates in ipilimumab-treated melanoma patients (Fig. 3A; refs. 20–22). An ALC ≥ 1,000/μL of whole blood (vs. ALC < 1,000/μL of whole blood) before the third...
infusion of ipilimumab, 10 mg/kg body weight, in patients with chemotherapy-refractory melanoma predicted for higher 6-month (75% vs. 0%) and 12-month (47% vs. 0%) survival rates (20–22). Also, an AEC increase >100/μL of whole blood between the first two ipilimumab infusions was associated with a longer median survival (11.3 months vs. 6.8 months; ref. 22). We observed that the ALC increased after radiotherapy and ipilimumab treatment (1,100/μL of whole blood at baseline, 2,700/μL of whole blood at peak levels, and 2,200/μL of whole blood before the third infusion of ipilimumab) and that the AEC increased between the first two infusions of ipilimumab (200/μL of whole blood before the first infusion and 470/μL of whole blood before the second infusion of ipilimumab; Fig. 3A). In addition, the posttreatment carcinoembryonic antigen levels (a nonspecific tumor marker) showed a dramatic drop to normal levels after a peak of 119.6 ng/mL (Fig. 3B).

Although the tumor markers remained at normal levels, a PET/CT on April 2013 showed an isolated increase in metabolic activity of a new nonirradiated left supraclavicular lymph node. The lymph node was excised and was found to have persistent disease. However, to our surprise, this specimen exhibited distinct immunologic differences in comparison with the previously excised left supraclavicular lymph node from 2010. Upon staining with hematoxylin and eosin, lymphocytic infiltration was largely confined to perivascular areas in the 2010 biopsy, whereas the biopsy from 2013 showed lymphocyte infiltration into the tumor cell nests (Fig. 4A). On further immunohistochemical analysis with CD8 (a marker for CTLs) and TIA-1 (a marker for cytotoxic granules) stains, the specimen from 2013 showed a marked increase in CD8+ and TIA+ cells (Fig. 4A and B). In addition, FoxP3+ (a marker for regulatory T cells) was also increased in the 2013 specimen, although the ratio of CD8+ /FoxP3+ cells was much higher in the 2013 specimen (Fig. 4B).

An increased ratio of effector to regulatory T cells following anti-CTLA-4 treatment is a hallmark of successful tumor rejection (23). The persistence of tumor cells in this lesion suggests the possibility for the development of adaptive resistance mediated by tumor cell upregulation of ligands inhibitory to T cells (14). Importantly, the detected PET/CT signal in the excised lesion, although nonspecific, could be caused by both heightened antitumoral inflammation and the proliferation of tumor cells, suggesting a need for caution in the interpretation of such signals in patients following immunotherapy (13).

After excision of the newly hypermetabolic left supraclavicular lymph node, the patient underwent further systemic treatment with ipilimumab alone. From June 2013 to August 2013, the patient received an additional four cycles of ipilimumab, 3 mg/kg given every 3 weeks. In September 2013, 1 year after treatment with concurrent radiotherapy and ipilimumab, the patient’s new PET/CT showed no evidence of disease (Fig. 5).

Discussion

Historically, abscopal responses are of rare occurrence. Few cases have been reported in several tumor types, including melanoma, renal cell carcinoma, and lymphoma (17, 18, 24–26). The remarkable abscopal response seen in this patient after treatment with local radiotherapy and ipilimumab is consistent with data in preclinical models that this combination can induce therapeutically effective antitumor immune responses to poorly immunogenic carcinomas (5, 8, 16). In the 4T1 mouse model, tumor-specific CD8+ T cells were responsible for tumor regression. The synergy between radiotherapy and anti-CTLA-4 antibody was at least in part due to improved recruitment of these effector T cells to the tumor and their enhanced interaction with tumor cells via NKG2D receptor engagement (16, 27). In addition, tumor-specific CD8+ T cells were expanded in mice treated with radiotherapy and anti-CTLA-4 antibody, consistent with the ability of radiotherapy to generate an in situ tumor vaccine (28).

Recently, an abscopal response was reported in a patient with NY-ESO-1 (cancer-testis antigen)–positive melanoma treated with local radiotherapy in combination with ipilimumab (17). The patient received ipilimumab at a dose of 10 mg/kg body weight every 3 weeks, for a total of four doses, as part of her induction therapy. Her follow-up CT scan showed overall stable disease. Nevertheless, while on maintenance ipilimumab (given every 12 weeks), the patient showed radiographic evidence of disease progression. Specifically, there was growth of a paraspinal mass, causing her right-sided back pain. However, when local radiotherapy (28.5 Gy in three fractions over a period of 7 days) was administered to the paraspinal metastasis, concurrently with maintenance ipilimumab, an abscopal response was detected 4 months later. Concurrent treatment led to the regression of distant disease in the spleen and mediastinal lymph nodes.
Interestingly, the therapeutic response temporarily correlated with an increase in antibody titers targeting epitopes in the central portion of NY-ESO-1 and other tumor-associated antigens, an increase in CD4+ T-cell and myeloid lineage activation, and a decline in the quantity of myeloid-derived suppressor cells.

Herein, we report the first abscopal response seen 2.5 months after the start of treatment with ipilimumab and fractionated radiotherapy in a patient with chemotherapy-refractory metastatic adenocarcinoma of the lung. We treated this patient with a radiotherapy dose and fractionation schedule similar to that used to convert tumor cells into an in situ vaccine and generate an abscopal response in our preclinical model (5). Although CTLA-4 blockade as a monotherapy or given as a concurrent regimen with chemotherapy did not lead to a benefit in PFS, the possibility that ipilimumab alone might be responsible for this patient’s response cannot be ruled out (12, 15). Nevertheless, this case report supports the belief that a combination of local radiotherapy and immunotherapy might prove to be a useful strategy to improve the outcomes of some patients with metastatic disease that are historically known to have dismal prognoses (3). In conclusion, this approach in NSCLC and other types of cancer represents a new paradigm worthy of establishing clinical trials for patients with advanced disease.

Disclosure of Potential Conflicts of Interest
S.C. Formenti is a consultant/advisory board member for Bristol-Myers Squibb. No potential conflicts of interest were disclosed by the other authors.

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