Concurrent Radiotherapy and Ipilimumab Immunotherapy for Patients with Melanoma

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Abstract
Ipilimumab and radiotherapy are commonly used to treat unresectable and metastatic melanoma. Results from preclinical studies and case reports suggest a biologic interaction between these two treatments. To understand the clinical implications of the interaction, we carried out a retrospective study reviewing records of patients treated with ipilimumab and radiotherapy for melanoma at our institution between 2005 and 2011. The review included details of treatment, response, adverse events (AE), and overall survival (OS). Twenty-nine patients underwent 33 courses of non-brain radiotherapy between their first and last dose of ipilimumab. Immune-related AEs (ir-AEs) were observed in 43% of patients receiving ipilimumab at 10 mg/kg and in 22% of patients receiving 3 mg/kg; the frequency of ir-AEs was not significantly different compared with previous studies of ipilimumab alone. Radiotherapy-related AEs were significantly more common in patients receiving higher doses of radiation. Palliation of symptoms was reported by 77% of patients after radiotherapy. Median OS was 9 and 39 months in patients receiving radiotherapy during induction and maintenance with ipilimumab, respectively. In this retrospective study, concurrent ipilimumab and radiotherapy was neither associated with higher than expected rates of AEs nor did it abrogate palliative effects of radiotherapy or survival benefits of ipilimumab. Further studies to prospectively explore the efficacy of this therapeutic combination are warranted. Cancer Immunol Res; 1(2): 92–98. ©2013 AACR.

Introduction
Ipilimumab is a monoclonal antibody that blocks cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), a negative regulator of T-cell function, which is essential for maintaining immunologic homeostasis. By blocking CTLA-4, ipilimumab disinhibits T cells and increases the immune response to cancer. Ipilimumab was approved in March 2011 by the U.S. Food and Drug Administration (FDA) for treatment of patients with unresectable and metastatic melanoma based on results from two randomized controlled trials showing an improvement in overall survival (OS). Although response rates are modest (10–15%), ipilimumab is a standard management strategy for metastatic and unresectable melanoma (1, 2).

Radiotherapy is used frequently in the management of metastatic melanoma. A recent study estimated that 45% of patients with metastatic melanoma receive radiotherapy during the course of their disease (3). A prospective study reported that palliative radiotherapy can be given to relieve symptoms (pain, neurologic impairment, hemorrhage, obstruction, dyspnea, or cough) or to prevent impending symptoms (pain, neurologic impairment, ulceration, or obstruction). Radiotherapy relieves pain in two-thirds of treated patients with melanoma (4).

Radiotherapy may modulate the immunotherapeutic effects of CTLA-4-blockade by ipilimumab. In a murine mammary carcinoma model, CTLA-4 blockade alone did not affect tumor growth or survival. However, when CTLA-4 blockade was combined with tumor radiotherapy, OS improved significantly. This effect seemed to be dependent on CD8⁺ T and invariant natural killer cells (5). Results from a follow-up study indicated that hypofractioned high-dose radiotherapy was necessary to elicit antitumor immune effects (6).

Little is known about the clinical effects of combining ipilimumab and radiotherapy. Previous studies reported high rates of adverse events (AE) when radiotherapy was combined with other immunotherapies, such as interferon (7–9). Moreover, lymphocytes are exquisitely sensitive to radiotherapy. As ipilimumab affects lymphocytes directly, radiotherapy could potentially diminish the immunotherapeutic effects. Two recent case reports showed remarkable responses to ipilimumab only after non-brain radiotherapy treatment...
This result supports the preclinical work described above and suggests synergy of this combination approach. Results from case series of palliative brain radiotherapy combined with ipilimumab for patients with metastatic melanoma have also indicated synergy (12–15). Therefore, we conducted a systematic, retrospective analysis of the toxicity and efficacy of ipilimumab and non-brain radiotherapy in records of patients with melanoma. The goal of the study was to analyze the safety profile of non-brain radiotherapy given during ipilimumab immunotherapy to establish a foundation for prospective trials assessing the efficacy of this promising combination for patients with melanoma.

Materials and Methods

Patients

Medical record review was conducted with permission of the institutional review board (WA0194-11). Patients with unresectable stage III and stage IV melanoma, who received ipilimumab immunotherapy between February 21, 2005 and August 16, 2011, were identified in our institutional databases. Among this group of patients, those who received treatment with non-brain radiotherapy between the first and last dose of ipilimumab were chosen for the study. Demographic information on patient, disease, and treatment characteristics at the time of starting ipilimumab (sex, age, type of melanoma, time since initial diagnosis of melanoma, presence of visceral or brain metastases, lactate dehydrogenase, courses of prior systemic and radiotherapies) were used for the analysis.

Therapy and adverse events

Medical record review focused on details of dose, date, and phase of ipilimumab administration. Radiotherapy was delivered during the induction or maintenance phase of ipilimumab administration. During the induction phase, radiotherapy occurred between the first and fourth doses of ipilimumab, or within 16 weeks of starting ipilimumab; during the maintenance phase, radiotherapy began after the last induction dose more than 16 weeks after starting ipilimumab. Common terminology criteria for AEs (CTCAE v4.0) grade 3 or higher immune-related AEs (ir-AEs) were recorded. Radiotherapy record review focused on details including the target of treatment, treatment intent, total dose, fractionation, and dates of treatment. Equivalent radiation doses for melanoma in 2 Gy fractions (EQD2) were calculated using the α/β of melanoma (0.6). Irradiated organs were assessed for CTCAE (v4.0) grade 3 or higher AEs. Average absolute lymphocyte count (ALC) during the 12-week period before and after the initiation of radiotherapy was recorded.

Treatment response

The local effect of radiotherapy was recorded (in-field disease control for postoperative radiotherapy, improvement, or prevention of symptoms for palliative radiotherapy). Given the heterogenous and delayed responses to ipilimumab, we focused on efficacy analyses of time to treatment failure (TTF) and OS (16). TTF was defined as the interval from ipilimumab start to last follow-up, death, or the start of a different systemic therapy. OS was defined as the interval from ipilimumab start to last follow-up or death.

Statistical analysis

Summaries of the statistical analysis are presented. Fisher exact test was used to calculate differences in the frequency of grade ≥3 AEs (two-sided, α = 0.05). A paired t test (two-sided, α = 0.05) was used to compare average ALC before and after radiotherapy. Kaplan–Meier methods were used to estimate TTF and OS. Statistical analyses were conducted using WinSTAT for Microsoft Excel, version 2009.1.

Results

Patients

Between February 21, 2005 and August 16, 2011, 333 patients received ipilimumab immunotherapy for melanoma at our institution (Fig. 1). Half (49.8%) of these patients also received linear accelerator-generated radiotherapy for melanoma. Many patients received several courses of brain and non-brain radiotherapy before, during, and after ipilimumab treatment. Radiotherapy was most frequently given to non-brain targets.
Twenty-nine patients (8.7%) underwent 33 courses of non-brain radiotherapy between the first and last dose of ipilimumab. One patient (#21) received radiotherapy during induction and maintenance phases of ipilimumab. Most patients (22.5%) underwent non-brain radiotherapy before the first dose of ipilimumab, whereas other patients (13.5%) underwent non-brain radiotherapy after receiving the last dose of ipilimumab. Median follow-up of all patients after starting ipilimumab was 11 months. Median follow-up of survivors after starting ipilimumab was 34 months.

Characteristics of patients receiving radiotherapy during ipilimumab treatment are presented in Table 1. Most patients were male, with recurrent, previously treated, metastatic cutaneous melanoma at the time of starting ipilimumab. Few patients had brain metastases when starting ipilimumab, but most had visceral metastases.

### Treatment and adverse effects

The median doses of ipilimumab and radiotherapy were 10 mg/kg and 30 Gy, respectively. Most patients (69%) were treated on ipilimumab research protocols (CA184045, CA184087, CA184088, CA184078, CA184022, CA184042, and CA209004). Table 2 describes treatment parameters among patients experiencing a grade ≥3 AE.

<table>
<thead>
<tr>
<th>Table 1. Patient and disease characteristics</th>
<th>Radiotherapy during induction ipilimumab (n = 18 patients)</th>
<th>Radiotherapy during maintenance ipilimumab (n = 11 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
<td>14</td>
</tr>
<tr>
<td>Female</td>
<td>4</td>
<td>3^a</td>
</tr>
<tr>
<td>Age at start of ipilimumab, y</td>
<td>Median (range)</td>
<td>60 (21–77)</td>
</tr>
<tr>
<td>Melanoma origin</td>
<td>Cutaneous</td>
<td>12</td>
</tr>
<tr>
<td>Uveal</td>
<td>2</td>
<td>1^a</td>
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<tr>
<td>Mucosal</td>
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<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Interval from diagnosis to M/R recurrence, mo</td>
<td>Median (range)</td>
<td>11 (0–74)</td>
</tr>
<tr>
<td>Courses of therapies for M/R melanoma before ipilimumab</td>
<td>Systemic</td>
<td>Median (range)</td>
</tr>
<tr>
<td>Non-brain radiotherapy</td>
<td>Median (range)</td>
<td>0 (0–1)</td>
</tr>
<tr>
<td>At start of ipilimumab</td>
<td>ECOG performance status</td>
<td></td>
</tr>
<tr>
<td>0</td>
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<td>2</td>
</tr>
<tr>
<td>1</td>
<td>17</td>
<td>9^a</td>
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<tr>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Brain metastasis</td>
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<td>13</td>
</tr>
<tr>
<td>Yes</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Visceral metastasis</td>
<td>No</td>
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<tr>
<td>Yes</td>
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<td>10^a</td>
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<tr>
<td>Lactate dehydrogenase (IU/L)</td>
<td>Median</td>
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</tr>
<tr>
<td>Range</td>
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<td>154–599</td>
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<tr>
<td>AJCC M stage</td>
<td>M0 (unresectable)</td>
<td>2</td>
</tr>
<tr>
<td>M1a</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>M1b</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>M1c</td>
<td>14</td>
<td>9^a</td>
</tr>
</tbody>
</table>

Abbreviations: AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; M/R, metastatic/unresectable.

^aIncludes one patient that received radiotherapy during induction and maintenance ipilimumab.
<table>
<thead>
<tr>
<th>Patient number</th>
<th>Ipilimumab treatment dose (mg/kg)</th>
<th>Cumulative ipilimumab dose (mg/kg)</th>
<th>Cumulative ipilimumab dose (mg/kg) at start of radiotherapy</th>
<th>Phase of ipilimumab radiotherapy given</th>
<th>RT (Gy)</th>
<th>Number of radiotherapy fractions</th>
<th>EQD2 (0.6)</th>
<th>Radiotherapy site</th>
<th>Grade ≥3 AE</th>
<th>Time from ipilimumab start to AE (days)</th>
<th>Time from radiotherapy start to AE (days)</th>
<th>AE Attribution</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>40</td>
<td>10</td>
<td>Induction</td>
<td>24</td>
<td>1</td>
<td>227</td>
<td>T12 Vertebral metastasis</td>
<td>Grade 3 cytokine release</td>
<td>7</td>
<td>3</td>
<td>ir and/or rr</td>
</tr>
<tr>
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<td>10</td>
<td>40</td>
<td>10</td>
<td>Induction</td>
<td>24</td>
<td>1</td>
<td>227</td>
<td>T7 Vertebral metastasis</td>
<td>Grade 3 cytokine release</td>
<td>7</td>
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</tr>
<tr>
<td>3</td>
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<td>6</td>
<td>3</td>
<td>Induction</td>
<td>25</td>
<td>10</td>
<td>30</td>
<td>Left base of skull tumor</td>
<td>Grade 3 diathesis</td>
<td>36</td>
<td>32</td>
<td>ir</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>40</td>
<td>10</td>
<td>Induction</td>
<td>30</td>
<td>10</td>
<td>42</td>
<td>Right humeral metastasis</td>
<td>Grade 3 transaminase elevation</td>
<td>104</td>
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<td>ir</td>
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<td>20</td>
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<td>62.5</td>
<td>25</td>
<td>75</td>
<td>Left axillary lymphadenopathy</td>
<td>Grade 3 transaminase elevation and rash</td>
<td>63</td>
<td>94</td>
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<td>6</td>
<td>Induction</td>
<td>30</td>
<td>10</td>
<td>42</td>
<td>Conus medullaris metastasis</td>
<td>Grade 3 maculopapular rash b</td>
<td>98</td>
<td>64</td>
<td>ir</td>
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<td>13</td>
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<td>12</td>
<td>6</td>
<td>Induction</td>
<td>28.5</td>
<td>3</td>
<td>111</td>
<td>Sacral metastasis</td>
<td>Grade 3 thrombocytopenia</td>
<td>50</td>
<td>22</td>
<td>rr</td>
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<tr>
<td>15</td>
<td>3</td>
<td>9</td>
<td>6</td>
<td>Induction</td>
<td>30</td>
<td>3</td>
<td>122</td>
<td>Right suboccipital lymphadenopathy</td>
<td>Grade 3 transaminase elevation</td>
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<td>160</td>
<td>30</td>
<td>Induction</td>
<td>20</td>
<td>5</td>
<td>35</td>
<td>Base of skull metastasis a</td>
<td>Grade 4 uveitis</td>
<td>1,186</td>
<td>1,126</td>
<td>ir and/or rr</td>
</tr>
<tr>
<td>22</td>
<td>10</td>
<td>110</td>
<td>80</td>
<td>Maintenance</td>
<td>28.5</td>
<td>3</td>
<td>111</td>
<td>T7 Vertebral metastasis</td>
<td>Grade 3 radiculitis</td>
<td>927</td>
<td>477</td>
<td>rr</td>
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<tr>
<td>24</td>
<td>10</td>
<td>170</td>
<td>160</td>
<td>Maintenance</td>
<td>30</td>
<td>10</td>
<td>42</td>
<td>Upper abdominal lymphadenopathy</td>
<td>Grade 3 pruritus</td>
<td>1,326</td>
<td>293</td>
<td>ir</td>
</tr>
<tr>
<td>29</td>
<td>10</td>
<td>50</td>
<td>30</td>
<td>Maintenance</td>
<td>30</td>
<td>5</td>
<td>76</td>
<td>Right hilar lymphadenopathy</td>
<td>Grade 3 transaminase elevation</td>
<td>41</td>
<td>(Before radiotherapy)</td>
<td>ir</td>
</tr>
</tbody>
</table>

Abbreviations: EQD2, equivalent dose in 2 Gy fractions with α/β of 0.6; ir, immune related; rr, radiation related.

aSecond course of radiotherapy to this site.

bRash occurred outside radiotherapy field, after vemurafenib.
Grade ≥3 ir-AEs were more frequent in patients receiving ipilimumab at 10 mg/kg (43%) than at 3 mg/kg (20%; Supplementary Table S1). Comparing the present data with historic results, statistical analysis using Fisher exact test did not show significant difference in the frequency of grade ≥3 ir-AEs at 3 mg/kg ($P = 0.70$), or at 10 mg/kg ($P = 0.20$; refs. 1, 17).

The frequency of grade ≥3 AEs in irradiated organs was 15% for the 33 courses of radiotherapy given during ipilimumab treatment. One grade 4 event was noted in a previously irradiated organ that was reirradiated. Among patients not having the same target reirradiated, EQD2(0.6) more than 100 Gy was associated with radiation-related AEs by Fisher exact test (44% vs. 0%, $P = 0.004$).

Average ALC decreased after 27 of 33 courses (82%) of radiotherapy. The average ALC was significantly lower after radiotherapy (0.93 k/μL) than before radiotherapy (1.34 k/μL, $P < 0.005$).

Local treatment response, TTF, and OS

Symptom alleviation was noted after 17 of 22 (77%) courses of radiotherapy given for palliation; 3 patients were not reassessed for symptoms after radiotherapy and 2 patients experienced symptom progression. None of the 9 patients treated to prevent symptoms from metastatic melanoma developed symptoms. Two patients underwent postoperative radiotherapy after resection of metastatic melanoma and did not develop locoregional recurrence with follow-up of 5 and 56 months.

Twelve patients (41%) were treated with a different systemic therapy after receiving ipilimumab and radiotherapy, following clinician-determined treatment failure. Nine of the 19 patients (47%) receiving radiotherapy during the induction phase of ipilimumab treatment changed systemic therapy and 3 of 11 (27%) receiving radiotherapy during the maintenance phase of ipilimumab treatment also changed systemic therapy. Median TTF was 5 months for patients undergoing radiotherapy during induction ipilimumab and 39 months for patients undergoing radiotherapy during maintenance ipilimumab. Median OS was 9 months for patients undergoing radiotherapy during induction ipilimumab and 39 months for patients undergoing radiotherapy during maintenance ipilimumab (Fig. 2).

Discussion

This study was designed to assess the safety of concurrent non-brain radiotherapy and ipilimumab immunotherapy in patients with melanoma. Prior research suggested that radiotherapy during immunotherapy might be associated with high rates of AEs (7–9). Moreover, CTLA-4 blockade targets lymphocytes, which are known to be exquisitely sensitive to radiation, but it was not known whether radiotherapy might compromise the benefit of ipilimumab treatment. We found that the rates of local AEs or systemic ir-AEs were not increased with concurrent radiotherapy and ipilimumab treatment. Furthermore, combining these treatments did not compromise the local and survival benefits of radiotherapy and ipilimumab, respectively.

![Figure 2. Overall survival in patients undergoing radiotherapy (RT) during induction or maintenance ipilimumab (Ipi) immunotherapy. OS was calculated from time of start of ipilimumab to time of death or last follow-up.](image-url)
Radiotherapy and Ipilimumab for Melanoma

Radiotherapy and Ipilimumab for Melanoma

...necessary to better understand the signifi-
...apy, there did not appear to be a negative effect on survival after 
...apy. However, despite a reduction in the ALC after radiother-
...reduction in 12-week average ALC was noted after radiother-
...myelophenopenia, we explored the changes in ALC after 
...y, there did not appear to be a negative effect on survival after 
....Future studies to characterize the immunologic response to radiotherapy and ipilimumab are necessary to better understand the significance of this finding.

The local symptomatic response to palliative radiotherapy in the present study was 77%, which is consistent with a 67% response rate found in a previous study of palliative radiotherapy for patients with metastatic melanoma (4). Postoperative locoregional radiotherapy was used infrequently among the present cohort, but no recurrences were noted in the irradiated targets, suggesting successful locoregional disease control.

Median OS of 9 months after radiotherapy during induction ipilimumab is comparable with the median survival of patients with unresectable or metastatic melanoma that failed a prior therapy and were treated with ipilimumab (3 mg/kg) alone (10.1 months, 95% confidence interval, 8.0–13.8 months; ref. 1). However, median OS among those receiving radiotherapy during maintenance ipilimumab (at 10 mg/kg) was 39 months. Previous studies have suggested longer OS in patients receiving ipilimumab at 10 mg/kg (median OS of 17.7–19.3 months), although studies comparing survival at these two doses are still ongoing (NCT01515189; ref. 18). The greater than expected median OS in patients receiving radiotherapy during maintenance ipilimumab is probably due to selection bias introduced by the protocol requirements. Maintenance therapy is not offered outside of a clinical trial and is not included in the FDA label for ipilimumab. However, the finding is provocative and suggests that if radiotherapy modifies the effect of ipi-

The present analysis has several limitations. First, the retro-

Authors’ Contributions

Conception and design: C.A. Barker, M.A. Postow, Y. Yamada
Development of methodology: C.A. Barker, M.A. Postow, Y. Yamada
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): C.A. Barker, M.A. Postow, K. Beal, Y. Yamada, N.Y. Lee, J.D. Wolchok
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): C.A. Barker, M.A. Postow, N.Y. Lee, J.D. Wolchok
Writing, review, and/or revision of the manuscript: C.A. Barker, M.A. Postow, K. Beal, P.K. Parhar, Y. Yamada, N.Y. Lee, J.D. Wolchok
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): C.A. Barker, S.A. Khan, J.D. Wolchok
Study supervision: C.A. Barker

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