Increased treatment-related toxicity subsequent to an anti–PD-1 agent

The Editor
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The approval of ipilimumab¹ and, subsequently, the BRAF inhibitors vemurafenib² and dabrafenib³ for the treatment of metastatic melanoma has improved survival in this hitherto often fatal disease. However, resistance to those agents limits efficacy. The KEYNOTE-001 phase I study evaluated the use of pembrolizumab, an anti–PD-1 antibody in metastatic melanoma, in treatment-naïve and refractory disease. A range of doses and schedules were evaluated: 2 mg/kg 3 weekly, 10 mg/kg 3 weekly, and 10 mg/kg 2 weekly⁴–⁶. Efficacy and safety with all doses were similar and favourable. Pembrolizumab (2 mg/kg every 3 weeks) is now approved by the U.S. Food and Drug Administration for treatment-refractory metastatic melanoma, providing a further line of therapy in a difficult-to-treat population.

Recently, preliminary results from the first-line KEYNOTE-006 phase III trial (comparing pembrolizumab at 10 mg/kg on 2 weekly and 3 weekly schedules with ipilimumab as the standard arm) showed superior survival in pembrolizumab-treated patients⁷. Given the significant activity of first-line pembrolizumab, it is likely that this drug will be used earlier in a patient’s treatment trajectory. The optimum sequencing of immunotherapy and targeted therapy is yet to be determined⁸.

Decisions about the sequencing of the anti–PD-1 antibodies—either off-trial or after trial enrolment once disease progression occurs—currently remain unclear. We treated 8 patients on the phase I trial with pembrolizumab, a high-affinity human immunoglobulin G4 monoclonal antibody against PD-1, with a half-life of 2–3 weeks. All 8 patients were later switched to other agents on disease progression: 3 patients were BRAF-mutant and received vemurafenib; 5 were BRAF-negative and received ipilimumab (Table I details patient characteristics and treatment toxicities). Of the 3 BRAF-mutant patients, all 3 had a grade 3 maculopapular rash that occurred within 4 weeks of stopping pembrolizumab and starting vemurafenib. Vemurafenib was discontinued, and all 3 were treated with high-dose steroids (1 patient also had concurrent grade 2 pyrexia requiring inpatient care). The rash completely resolved over 2 weeks, and treatment with dabrafenib was started thereafter in 2 patients. One patient had no recurrence of toxicity, but another developed possible Guillain–Barré syndrome (and remains under investigational workup) 2 months later (3 months after stopping pembrolizumab). The third patient restarted vemurafenib at a reduced dose of 720 mg twice daily, which was well tolerated. In the patients that went on to receive ipilimumab, 4 of 5 had immune-related side effects of fevers, diarrhea (with 1 case of colitis requiring infliximab treatment), and hepatitis. Additionally, 1 patient had a 24-hour episode of unexplained encephalopathy that spontaneously resolved within 48 hours in hospital. Those toxicities all occurred within 7 weeks of treatment—that is, within the 1st or 2nd cycle of treatment with ipilimumab. Of the 8 patients described, 3 had an immune-related side effect with pembrolizumab: thyroiditis that progressed to hypothyroidism requiring treatment by week 8 of pembrolizumab therapy. Autoantibody profiling (for thyroid and antinuclear antibodies during treatment with pembrolizumab) did not correlate with development of toxicity either on pembrolizumab or on subsequent agents (data not shown). Of our patients reported here, 2 received 2 mg/kg every 3 weeks, the dose going forward for the treatment of metastatic melanoma.

Grade 3 rash is not uncommon with single-agent vemurafenib. The incidence of grade 3 rash in the BRIM 3 trial was 8%⁹. Skin toxicities are reported to be lower with dabrafenib than they are with vemurafenib, and maculopapular rashes were not reported in the BREAK-3 trial¹⁰. As in our experience, the increased incidence of rash was seen in patients sequentially treated with ipilimumab and then vemurafenib, where patients were successfully re-challenged with vemurafenib at lower doses⁴. Increased toxicity with vemurafenib has also been reported post nivolumab, another PD-1 inhibitor, and skin biopsies in those patients showed a dermal hypersensitivity reaction¹¹. Now that dabrafenib is also a standard of care, the choice of a BRAF-targeted therapeutic could be dictated by its toxicity profile. Although immune-related toxicities are well documented with ipilimumab, the incidence of several toxicities in the same patient is more unusual. Neurologic toxicities—most commonly neuropathies and case reports of aseptic meningitis or encephalopathy—secondary to ipilimumab alone have been reported¹².

The mechanisms dictating increased toxicity with vemurafenib post anti–PD-1 treatment are unclear. There is evidence to show increased tumour infiltration after BRAF inhibition¹³. An activated immune response by PD-1 inhibition before either vemurafenib or ipilimumab might well result in increased immunomodulation and toxicity thereof. Trials are ongoing with respect to combinations of checkpoint inhibitors either alone (https://clinicaltrials.gov/ct2/show/NCT01844505) or in combination with targeted agents such as dabrafenib and trametinib (https://clinicaltrials.gov/ct2/show/NCT01767454), and

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in sequencing (https://clinicaltrials.gov/ct2/show/NCT01673854). Although our patient numbers are small and the findings here observational, our experience suggests that toxicity might be increased with subsequent treatments after an anti-PD-1 antibody.

<table>
<thead>
<tr>
<th>Pt ID</th>
<th>Sex</th>
<th>Age</th>
<th>Stage</th>
<th>Doses (n)</th>
<th>Pembrolizumab treatment</th>
<th>Subsequent treatment</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>31</td>
<td>M1c</td>
<td>2</td>
<td>Yes: thyroiditis followed by hypothyroidism</td>
<td>Vemurafenib, Rash, grade 3</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>81</td>
<td>M1c</td>
<td>6</td>
<td>Yes: thyroiditis followed by hypothyroidism</td>
<td>Vemurafenib, switched to dabrafenib, Rash, grade 3; Guillain–Barré—like syndrome (under investigation) occurred 2 months after rash</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>43</td>
<td>M1c</td>
<td>5</td>
<td>No</td>
<td>Vemurafenib, switched to dabrafenib, Rash, grade 3; fevers, grade 2</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>47</td>
<td>M1c</td>
<td>8</td>
<td>No</td>
<td>Ipilimumab, 2 treatments, Hepatitis, grade 2; fevers, grade 2; encephalopathy, grade 3 (lasting 24 hours only)</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>64</td>
<td>M1c</td>
<td>6</td>
<td>No</td>
<td>Ipilimumab, 1 treatment, Hepatitis, grade 1; fevers, grade 2; diarrhea, grade 3</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>53</td>
<td>M1c</td>
<td>9</td>
<td>Yes: thyroiditis followed by hypothyroidism</td>
<td>Ipilimumab, 1 treatment, Fever, grade 1; diarrhea, grade 2; hepatitis, grade 2</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>52</td>
<td>M1c</td>
<td>4</td>
<td>No</td>
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<td>8</td>
<td>F</td>
<td>68</td>
<td>M1c</td>
<td>12</td>
<td>2 mg/kg (3 weekly)</td>
<td>Ipilimumab, 4 treatments, None</td>
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</table>

**CONFLICT OF INTEREST DISCLOSURES**

We have read and understood Current Oncology’s policy on disclosing conflicts of interest, and we declare that we have none.

**REFERENCES**