CASE REPORT

Treatment of malignant melanoma with nivolumab and vemurafenib combined with hypofractionated radiation therapy

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Abstract Management of metastatic malignant melanoma is challenging. Although several new systemic therapies for metastatic malignant melanoma have recently been developed, some patients still also require radiation therapy (RT) for palliative care. However, the safety and efficacy of combining use of novel drugs with RT remain unclear. Here, we report treating a patient with rapidly growing malignant melanoma with a programmed cell death protein 1 (PD-1) inhibitor and a BRAF inhibitor together with 60 Gy of hypofractionated RT without severe adverse effects. The tumor within the radiation field exhibited a more marked response than that outside it. A combination of RT with an anti-PD-1 antibody or a BRAF inhibitor may, therefore, be a useful and tolerable approach to treating metastatic BRAF-mutant melanoma.

Keywords Melanoma · Hypofractionated radiation therapy · BRAF · Anti-PD-1 antibody

Introduction

Management of malignant melanoma is difficult, because this disease is resistant to radiation therapy (RT) and cytotoxic chemotherapy. Patients with metastatic melanoma reportedly achieve a median survival of only <12 months [1]. However, in the past 5 years, several novel systemic therapies for metastatic melanoma have been

developed; these include targeted inhibitors of the mitogen-activated protein kinase signaling pathway and immune checkpoint inhibitors directed against PD-1 and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) [2]. Despite these advances in systemic therapies, some patients develop recurrent or symptomatic disease. In such cases, RT may provide a palliative benefit and can occasionally extend the duration of local disease control [3]. However, the safety and synergistic effect of combining novel systemic therapies with RT are unclear.

Here, we report a patient with metastatic malignant melanoma whose primary tumor was assumed to be on the breast and whom we treated with an anti-PD-1 antibody and, subsequently, a BRAF inhibitor concurrently with hypofractionated RT.

Case report

A 62-year-old woman presented with enlarged lymph nodes in the left axilla and neck, biopsy of which revealed malignant melanoma. No primary site was identified; however, the distribution of lymph node metastases suggested that the primary tumor was on the breast, and the patient was staged as cTxN3M1 according to the criteria of the Union for International Cancer Control (seventh edition). We resected the affected axillary lymph nodes to achieve volume reduction and began treatment with dacarbazine and interferon. One month later, we found that the residual mass had enlarged (Fig. 1a). With this evidence of progressive disease, we changed the treatment to nivolumab, an anti-PD-1 antibody that blocks PD-1 signaling, at a dose of 2 mg/kg of body weight every 2 weeks. However, 10 days after initiation of nivolumab therapy, the axillary mass rapidly enlarged, and she had stabbing pain

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Fig. 1 Computed tomography (CT) images and timeline of therapy. Yellow arrows indicate mediastinal lesions and pleural effusion, white squares the radiation field, and yellow circles left breast lesions outside the radiation field. **a** Status before treatment with nivolumab. **b** Disease progressed at all sites during nivolumab and radiation therapy (RT). **c** CT images 1 week after completing RT (2 weeks after starting vemurafenib): all lesions show a response. **d** All lesions

have regressed significantly; however, there is new, enlarging, left breast lesion outside the radiation field. **e** CT images 3 months after RT, showing an enduring response within the radiation field but rapid progression of the left breast lesion outside the radiation field. **f** CT images several days before left mastectomy, when response has persisted only within the radiation field

in her left shoulder and arm, which was scored 8 points on the numerical rating scale (NRS; from 0, no pain to 10, worst possible pain) and could not be controlled by opioid analgesics. Therefore, we initiated hypofractionated RT administered in three fractions of 6 Gy per week. Because the safety of RT with nivolumab or vemurafenib has not been established, we excluded the lung and esophagus from the radiation fields as much as possible, which meant that some of the left breast lesions were not irradiated (Fig. 2).

Following administration of two doses of nivolumab, a positive BRAF mutation was identified. Because responses to immunotherapy are typically observed several months after initiation of treatment and the tumor had continued to grow rapidly and caused severe pain (Fig. 1b), we substituted the

BRAF inhibitor vemurafenib at a dose of 960 mg twice daily for nivolumab. Six weeks after commencing vemurafenib, a grade 3 increase in alanine aminotransferase concentration (according to the Common Terminology Criteria for Adverse Events version 4.0) was detected. Therefore, vemurafenib was discontinued for 2 weeks and then resumed at a dose of 720 mg twice daily. RT (up to 60 Gy) was continued during treatment with both nivolumab and vemurafenib with the aim of slowing tumor growth while minimizing adverse effects; however, grade 3 radiation dermatitis developed 3 days after completing RT (Fig. 3). This gradually resolved with oral and topical steroids. One month after completing RT, all lesions had regressed significantly and the pain decreased from NRS 8 to NRS 2 points and became acceptable for the patient

Fig. 2 A CT simulation image for radiotherapy planning. The target volume (indicated in red) encompasses the mass from the left neck to breast that is responsible for the patient's pain

(Fig. 1c). Three months after completion of RT, follow-up computed tomography (CT) revealed that the tumor had decreased in size within the radiation field and was close to stable in the mediastinum, which was outside the radiation field (Fig. 1e). However, a rapidly growing lesion was also detected on CT images in the left breast outside the radiation field (Fig. 1f). With this conclusive evidence that the tumor was resistant to the BRAF inhibitor (vemurafenib), we performed left mastectomy to reduce tumor volume before reinitiating nivolumab treatment. In spite of ongoing nivolumab, all lesions outside the radiation field progressed, and the patient died of respiratory failure 9 months after diagnosis.

Discussion

Here, we describe a case of malignant melanoma treated with a combination of hypofractionated RT with an anti-PD-1 antibody and, subsequently, a BRAF inhibitor

without severe adverse effects. Of note, the tumor in the radiation field showed a more marked response than the tumor that was not irradiated. The tumors outside the radiation field progressed during treatment with vemurafenib, the breast lesions growing more rapidly than the mediastinal lesions.

We administered a larger dose (60 Gy) than a palliative RT dose, because the masses were extremely large and rapidly growing, and there was a risk of complete brachial plexus injury. Although there is no consensus on dose fractionation for malignant melanoma, biological and clinical studies suggest that hypofractionated RT with large, single doses produces better results than the conventional fractionated RT [4] and >4 Gy per fraction may be optimal [3]. In addition, hypofractionated RT can produce an anti-tumor immune response. RT can upregulate MHC class I expression dose-dependently, and a single dose of at least 4 Gy is required [5]. When combined with immunotherapies, hypofractionated RT may be more effective than conventionally fractionated RT; however,

Fig. 3 Acute radiation dermatitis of the back

additional data are required to confirm this [6]. Moreover, hypofractionated RT can result in higher rate of late adverse effects than conventionally fractionated RT. Because survival of melanoma patients has improved with the introduction of new systemic therapies, late radiation-induced adverse effects should be more carefully considered when planning treatment. In the present case, the tumor showed good response to vemurafenib temporarily, and a total dose of 60 Gy could have been reduced.

PD-1, an inhibitory checkpoint molecule, regulates the balance between immune activation and tolerance [7]. The use of the anti-PD-1 antibody nivolumab has been shown to significantly improve survival of melanoma patients in multiple Phase III trials [8–10]. In addition, nivolumab has higher response rates and less toxicity than CTLA-4 blockade with ipilimumab [8], making it a good candidate for use with RT. In mice with intracranial glioma, a combination of an anti-PD-1 antibody and radiation reportedly significantly increases survival and achieves an abscopal response [11, 12]. However, there are a few clinical data regarding the efficacy and safety of combining RT with an anti-PD-1 antibody.

Vemurafenib, one of the most potent inhibitors of the kinase domain of mutant BRAF, prolongs survival of melanoma patients with tumors carrying V600 mutations [13]. BRAF inhibitors have been shown *in vitro* to have a radiosensitizing effect on BRAF-mutated melanoma cells [14]. However, there is no standard consensus concerning continuation of BRAF inhibitors during RT. Some case reports suggest that combining RT with BRAF inhibitors is associated with increased cutaneous and non-cutaneous toxicity, such as pneumonitis, anorectics, and liver toxicity [15–17], and therefore, recommend that RT be withheld

during treatment with BRAF inhibitors. In the present case, adverse effects may have been minimized by excluding the lung and esophagus from the radiation field. However, Hecht et al. [18] have reported that concomitant RT and BRAF inhibitor therapy is feasible and has acceptable toxicity. Interruption of systemic treatment can result in progression of non-irradiated lesions; in addition, the radiosensitizing effect may improve local tumor control. Whether or not to interrupt BRAF inhibitor therapy during RT should be considered case by case, according to the tumor location and prognosis. In any event, patients receiving vemurafenib with RT should be closely monitored because of the potential for increased toxicity.

Most patients treated with vemurafenib develop progressive disease [13]. However, there is no consensus on a treatment strategy for such disease progression, particularly in patients with heterogeneous tumors. Therefore, whether or not to administer local therapy to growing lesions is an individual decision. Continued treatment with a BRAF inhibitor beyond initial progression may prolong survival [19], but generally only in patients with a few metastases in whom a combination of local therapy and continued administration of a BRAF inhibitor may be effective. Furthermore, advances in effective systemic therapies have increased the threshold for administering local therapies in patients with systemic metastases. However, it is possible that reducing the number of residual melanoma cells minimizes development of resistance by reducing the number of cells that could develop resistance [20]. Being less invasive than surgery, RT presents a potential option for local treatment during systemic therapy.

In the present case, it is difficult to conclude which drug was more effective, nivolumab or vemurafenib. Although the tumor showed good response to vemurafenib, durability of response to vemurafenib was only 3 months. Moreover, it is possible that tumor progression observed during nivolumab treatment was pseudoprogression and that combination of nivolumab and RT resulted in durable response in the radiation field.

In conclusion, we treated a patient with malignant melanoma concurrently with hypofractionated RT and an anti-PD-1 antibody and subsequently a BRAF inhibitor without severe adverse effects. A combination of these therapies can be useful for treating metastatic BRAF-mutant melanoma. However, the safety, RT timing, sequence, and dose fractionation should be individually determined for each such patient.

Compliance with ethical standards

Disclosure of potential conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals For this type of study, formal consent is not required. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Tsao H, Atkins MB, Sober AJ (2004) Management of cutaneous melanoma. *N Engl J Med* 351:998–1012
2. Hao M, Song F, Du X et al (2015) Advances in targeted therapy for unresectable melanoma: new drugs and combinations. *Cancer Lett* 359:1–8
3. Overgaard J (1986) The role of radiotherapy in recurrent and metastatic malignant melanoma: a clinical radiobiological study. *Int J Radiat Oncol Biol Phys* 12:867–872
4. Seegenschmiedt MH, Keilholz L, Altendorf-Hofmann A et al (1999) Palliative radiotherapy for recurrent and metastatic malignant melanoma: prognostic factors for tumor response and long-term outcome: a 20-year experience. *Int J Radiat Oncol Biol Phys* 44:607–618
5. Reits EA, Hodge JW, Herberts CA et al (2006) Radiation modulates the peptide repertoire, enhances MHC class I expression, and induces successful antitumor immunotherapy. *J Exp Med* 203:1259–1271
6. Sharabi AB, Lim M, DeWeese TL et al (2015) Radiation and checkpoint blockade immunotherapy: radiosensitisation and potential mechanisms of synergy. *Lancet Oncol* 16:e498–e509
7. Topalian SL, Hodi FS, Brahmer JR et al (2012) Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med* 366:2443–2454
8. Larkin J, Chiarion-Sileni V, Gonzalez R et al (2015) Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med* 373:23–34
9. Robert C, Long GV, Brady B et al (2015) Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med* 372:320–330
10. Weber JS, D'Angelo SP, Minor D et al (2015) Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol* 16:375–384
11. Zeng J, See AP, Phallen J et al (2013) Anti-PD-1 blockade and stereotactic radiation produce long-term survival in mice with intracranial gliomas. *Int J Radiat Oncol Biol Phys* 86:343–349
12. Sharabi AB, Nirschl CJ, Kochel CM et al (2015) Stereotactic radiation therapy augments antigen-specific PD-1-mediated antitumor immune responses via cross-presentation of tumor antigen. *Cancer Immunol Res* 3:345–355
13. Chapman PB, Hauschild A, Robert C et al (2011) Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med* 364:2507–2516
14. Sambade MJ, Peters EC, Thomas NE et al (2011) Melanoma cells show a heterogeneous range of sensitivity to ionizing radiation and are radiosensitized by inhibition of B-RAF with PLX-4032. *Radiother Oncol* 98:394–399
15. Peuvrel L, Ruellan AL, Thillays F et al (2013) Severe radiotherapy-induced extracutaneous toxicity under vemurafenib. *Eur J Dermatol* 23:879–881
16. Forschner A, Zips D, Schraml C et al (2014) Radiation recall dermatitis and radiation pneumonitis during treatment with vemurafenib. *Melanoma Res* 24:512–516
17. Anker CJ, Ribas A, Grossmann AH et al (2013) Severe liver and skin toxicity after radiation and vemurafenib in metastatic melanoma. *J Clin Oncol* 31:e283–e287
18. Hecht M, Zimmer L, Loquai C et al (2015) Radiosensitization by BRAF inhibitor therapy—mechanism and frequency of toxicity in melanoma patients. *Ann Oncol* 26:1238–1244
19. Chan MM, Haydu LE, Menzies AM et al (2014) The nature and management of metastatic melanoma after progression on BRAF inhibitors: effects of extended BRAF inhibition. *Cancer* 120:3142–3153
20. Hirata E, Girotti MR, Viros A et al (2015) Intravital imaging reveals how BRAF inhibition generates drug-tolerant microenvironments with high integrin $\beta 1$ /FAK signaling. *Cancer Cell* 27:574–588