plays a significant role in radiation induced cell kill and NLR could be a useful biomarker.

In addition to these findings, the significant negative linear relationship between baseline NLR and PNI in this study reinforce the importance of nutrition in supporting a healthy immune balance. This is of particular significance in low resource settings where locally advanced cervical cancer is mostly prevalent. Poor nutrition, reflected by a considerable burden of anemia and protein energy malnutrition, is a major health problem in these regions. Consequently, the interaction between nutrition and immune balance and the resulting impact on radiation response assumes particular importance in this scenario.

Despite the limited sample size, the findings of this study emphasize on the need for further investigations for determining the strength of the association between NLR and clinical tumor response following chemoradiation in locally advanced cervical cancer. In conclusion, NLR offers an inexpensive yet effective tool in the clinic for alerting the clinician of the possible treatment outcome. A baseline NLR value higher than 5 significantly lowers the clinical complete response, and close monitoring of these women during treatment could offer early and effective salvage in the event of treatment failure.

Ethical statement

This study was performed after informed consent and in accordance with the Code of Ethics of the World Medical Association.

Disclosure statement

No potential conflict of interest was reported by the authors.

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LETTER TO THE EDITOR

The efficacy of platinum-based chemotherapy for immune checkpoint inhibitor-resistant advanced melanoma

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Background

Immune checkpoint inhibitors (ICIs) have been widely used as a first-line therapy for BRAF wild-type advanced melanoma, and they significantly improve the prognosis compared with chemotherapy [1–3]. However, an effective treatment for ICI-resistant melanoma has not been established. Furthermore, a

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Table 1. Characteristics and clinical outcome of carboplatin and paclitaxel administrated after immunotherapy.

Case	Age/sex	Subtype	ICI before CP	Courses of ICI	Best response	Days from ICI to CP	Sites of distant metastases	LDH at the initiation of CP (U/L)	Courses of CP	Best response	Vital status	PFS (months)	OS (months)
1	30/F	Nodular	1st: Nivo	9	PD	81	Lung, liver	150	2	PD	Dead	1.2	8.8
			2nd: Ipi	4	PD								
2	61/F	Mucosal (oral cavity)	1st: Nivo	9	PD	50	Lung	280	12	SD	Alive	10.9	13.6
			2nd: Ipi	4	PD								
3	65/M	Mucosal[a] (nasal cavity)	1st: Ipi	4	PD	15	_[b]	253	15	SD	Alive	10.9	14.8
			2nd: Nivo	15	SD								
4	39/M	Acral	Nivo	37	SD	16	Lung, skin, muscle	460	2	PD	Dead	1.4	2.8
5	62/F	Mucosal[a] (genital mucosa)	Nivo	16	SD	14	Lung, liver, peritoneum	254	3	PD	Alive	2.2	4.4
6	79/F	Acral	Nivo	5	PD	15	Bone, lung, liver, skin	263	4	PR	Alive	3.3	3.3
7	69/F	Mucosal[a] (genital mucosa)	Nivo	9	SD	29	Lung	182	6	PR	Alive	5.3	5.3

ICI: immune checkpoint inhibitor; CP: combination of carboplatin and paclitaxel; PFS: progression-free survival; OS: overall survival; nodular: nodular melanoma; mucosal: mucosal melanoma; acral: acral lentiginous melanoma; Nivo: nivolumab; Ipi: ipilimumab; PD: progressive disease; SD: stable disease; PR: partial response; LN: lymph node.

[a]Primary unresectable.

[b]Case 3 had skull base involvement with liquorrhea at the initiation of CP.

previous study reported that ipilimumab therapy followed by nivolumab therapy had a low response rate but a high risk of severe immune-related adverse events (irAEs) [4]. Considering the situation, it is important to evaluate the efficacy of salvage chemotherapy in ICI-resistant melanoma. Recent studies of other malignancies described the efficacy of chemotherapy after immunotherapy [5–8], but there have been no similar studies on advanced melanoma. We herein describe the response to a combination of carboplatin and paclitaxel (CP) therapy in advanced melanoma after progression on ICIs.

Patients and methods

This retrospective study included nine advanced melanoma patients who initiated CP therapy after progression on ICIs at our institution from February 2017 to May 2018. Of those, seven patients who had measurable metastatic lesions and had received at least two cycles of CP therapy were included in this study; we excluded two cases who had only one course of CP therapy without response evaluation. Carboplatin (area under the curve 4 or 5, Calvert formula) plus paclitaxel (175 mg/m^2) were administered intravenously once every four weeks. We determined the best response, overall survival (OS), progression-free survival (PFS) and adverse events (AEs) for each case. To evaluate the patients' responses and AEs, we performed computed tomography every 1–2 months and blood sampling at least once a week. Tumour response was defined according to the Response Evaluation Criteria in Solid Tumors version 1.1, and AEs were defined according to Common Terminology Criteria for Adverse Events version 5.0. This study was performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital.

Results

The attributes and responses of each case are given in Table 1. All the tumours were BRAF wild-type. The mean duration from last ICI administration to first CP therapy was 31.4 days (range: 14–81 days). As the best response to the CP therapy, two of the seven patients achieved partial response (PR), two of the seven patients had stable disease (SD) and three of the seven patients had PD. The mean OS and PFS were 7.6 months (range: 4.4–14.8 months) and 5.0 months (range: 1.2–10.9 months), respectively. Of the four mucosal melanoma patients in this study, one achieved PR and two had SD as the best response. Furthermore, the mean OS and PFS were 9.5 and 7.3 months, respectively.

Regarding AEs during CP therapy, alopecia, neuropathy and neutropenia were the most common AEs. Other AEs were one of arthralgia, one of fatigue, one of nausea and one of rash. In addition, one patient had interstitial pneumonia during ipilimumab therapy and then another drug-induced lung injury during CP therapy. The lung injury during CP therapy might be regarded as an immune-related AE (Supplementary Table S1). While grade 3/4 neutropenia was observed very frequently, it was manageable with injections

of granulocyte-colony stimulating factor in all patients, and none of them needed cessation of the treatment.

Discussion

There are no effective chemotherapies for melanoma. The response rate to dacarbazine single agent in large-scale studies is only about 5–12%, and only 1–2% of cases achieve a long-term response [9]. Recent studies in other fields show that the response rate of chemotherapy after ICI therapy equals or exceeds the response rate of chemotherapy before ICI therapy [5–8]. Of note, in non-small cell lung cancer treated with platinum-based chemotherapy, the response rate of salvage chemotherapy administered after ICI therapy is significantly greater than the response rate of the last chemotherapy before ICI therapy [5]. In our study in which platinum-based chemotherapy was administered to advanced melanoma patients, that administration also improved the response rate more than chemotherapy did in previous studies [1–3, 9]. Since the observation period was short, improvement in survival was not clearly shown. However, five of the seven patients survived to the end of observation.

Several studies have addressed the treatment of ICI-resistant melanoma, but no standard treatments are available. Blasig et al. described the reinduction of PD-1 inhibitor therapy after the failure of ICI therapy [10]. In their study, eight advanced melanoma patients who had already experienced ICI therapy were subsequently retreated with PD-1 inhibitor for a median of 2.5 months. As the best response in their cohort, one patient (12.5%) achieved PR and three patients (37.5%) had SD. In addition, Fujisawa et al. reported that the response rate to ipilimumab therapy after the failure of nivolumab therapy was only 3.6%; nevertheless, severe irAEs occurred in more than half of the participants [4]. Intriguingly, their study of 67 patients included 20 mucosal and 20 acral lentiginous melanoma patients. Other reports also indicated that the response rate and survival time were worse for mucosal and acral lentiginous melanoma than for other subtypes [11, 12]. The responses to ICIs in mucosal and acral lentiginous melanoma patients were also poor in our study; however, the response to chemotherapy tended to be relatively favorable. In the responses of four cases with controlled disease, one mucosal melanoma patient and one acral lentiginous melanoma patient achieved PR, and two mucosal melanoma patients had SD.

This study is limited because of its retrospective nature, the small sample size and the short observation period. Further, large-scale studies are required to confirm the efficacy of chemotherapy for ICI-resistant melanoma. In addition, we confirmed the development of distant new metastases or unequivocal progression of target lesions with at least two response evaluations during ICIs therapy. However, the possibility that the response to CP therapy was actually a late response to ICI treatment cannot be ruled out.

In conclusion, we reported cases treated with CP therapy after progression on ICI therapy. Although mucosal and acral lentiginous melanomas are known to respond poorly to ICI therapy, these clinical subtypes responded to CP therapy after ICI therapy in our study.

Disclosure statement

None to declare.

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