Translational Oncology 14 (2021) 100949

Contents lists available at ScienceDirect

Translational Oncology

journal homepage: www.elsevier.com/locate/tranon

Chemotherapy combined with antiangiogenic drugs as salvage therapy in advanced melanoma patients progressing on PD-1 immunotherapy

Xuan Wang, Writing - original draft; Writing - review & editing[1], Weiran Xu, Software; Visualization; Writing - original draft; Writing - review & editing[1], Zhihong Chi, Lu Si, Xinan Sheng, Yan Kong, Li Zhou, Lili Mao, Bin Lian, Bixia Tang, Xieqiao Yan, Xue Bai, Chuanliang Cui, Formal analysis; Data curation*, Jun Guo, Conceptualization; Methodology; supervision*

Key laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Renal Cancer and Melanoma, Peking University Cancer Hospital & Institute, 52 Fucheng Road, Haidian District, Beijing 100142, China

ARTICLE INFO

Keywords:
Melanoma
PD-1 inhibitor resistance
Chemotherapy
Antiangiogenic drugs
Nomogram

ABSTRACT

Background: This study aimed to evaluate the effect of salvage therapy with nab-paclitaxel (nab-p) or temozolomide (TMZ) combined with antiangiogenic drugs in programmed death 1 (PD-1) inhibitor-resistant patients with unresectable metastatic melanoma.

Methods: We conducted a retrospective review of 69 metastatic melanoma patients who received nab-p or TMZ combined with antiangiogenic drugs after developing PD-1 inhibitor resistance and were treated at the Beijing Cancer Hospital between 2016 and 2019. The disease control rate (c-DCR) and progression-free survival (c-PFS) of salvage CA (chemotherapy combined with antiangiogenic drugs) regimens were investigated. Univariate and multivariate analyses were performed to evaluate the clinical pathological factors affecting the outcomes. Then, a nomogram was formulated to predict the probability of 3-month and 6-month c-PFS based on the multivariate analysis results.

Results: The c-DCR was 63.8%, and the median c-PFS was 3.0 months. In the univariate analysis, factors associated with the c-DCR were included the melanoma subtype, baseline platelet-to-lymphocyte ratio (PLR) and best response status to PD-1 inhibitors. Factors influencing c-PFS included age, baseline lactic dehydrogenase, PLR, neutrophil-to-lymphocyte ratio (NLR), PFS duration of anti-PD-1 therapy (p-PFS), and the best response and progression pattern of PD-1 inhibitors. In the multivariate analysis, age <65 years, heterogeneous progression pattern and baseline PLR<200 were significantly associated with improved c-PFS. The concordance index (C-index) of the nomogram was equal to 0.65 (95% CI 0.566–0.734).

Conclusions: CA regimens demonstrated promising effects in PD-1 inhibitor-resistant patients. The nomogram could be a valuable predictive module for salvage therapy choice in PD-1 inhibitor-resistant patients.

Introduction

Patients with advanced melanoma exhibit poor prognoses. Checkpoint inhibitor therapy has led to a meaningful improvement in the response rate and survival for such patients [1], and programmed death 1 (PD-1) inhibitors have shown superior efficacy and safety compared with ipilimumab or traditional chemotherapy [2,3]. It is worth noting that all patients develop resistance to PD-1 inhibitors after initial treatment, which is a new obstacle to further improving the survival of patients with advanced melanoma. The underlying mechanisms of resistance are still not completely clear and likely involve the generation and function of anti-tumor T cells, the lack of neoantigens, suppression of antigen presentation, infiltration of other immunosuppressive cell populations and alteration of the tumor microenvironment (TME) [4].

Vascular endothelial growth factor (VEGF) plays an important role in the natural course of melanoma [5,6]. Anti-VEGF treatments are considered to be able to convert the immunosuppressive TME to an immune supportive TME, thus improving the outcome of immunotherapy [7]. Apatinib is a novel tyrosine kinase inhibitor that blocks the VEGF receptor-2, preventing VEGF binding and activation [8,9]. Endostatin is an endogenous angiogenesis inhibitor, which prevents tumor growth by controlling vascular formation [10]. Both drugs have demonstrated

* Corresponding authors.
E-mail address: 1008ccl@163.com (J. Guo).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.tranon.2020.100949
Received 23 August 2020; Received in revised form 31 October 2020; Accepted 5 November 2020

significant survival benefits with good tolerance [11] in patients with advanced melanoma.

The combination of antiangiogenic treatment and chemotherapy may lead to synergistic anti-tumor effects. A phase I study confirmed the effectiveness and safety of apatinib combined with temozolomide (TMZ) in patients with metastatic melanoma after the failure of conventional treatment, including a PD-1 inhibitor [12]. Moreover, nab-paclitaxel (nab-p) has been demonstrated to be effective in both previously treated and chemotherapy-naive patients with metastatic melanoma [13]. Treatment with nab-p could significantly improve the response rate and prolong progression free survival (PFS) with good safety compared with dacarbazine in phase III clinical trial [14].

Therefore, we conducted a retrospective study to examine the clinical efficacy of salvage therapy with nab-p or TMZ combined with antiangiogenic drugs (endostatin or apatinib) in PD-1 inhibitor-resistant patients with advanced melanoma.

Patients and methods

Patients

This study was a single-center retrospective observational study performed at Beijing Cancer Hospital. Patients treated between September 2016 and May 2019 were identified through the pharmacy database and electronic medical records. The inclusion criteria were as follows: (1) 18 years of age or older; (2) pathologically diagnosed with melanoma; (3) clinical stage IV (7th ed. AJCC/UICC); (4) treated with PD-1 inhibitor monotherapy, which was continued until either a radiographic tumor or overt clinical progression was observed; (5) and subsequent reception of nab-p/endostatin or TMZ/apatinib regimen after PD-1 inhibitor resistance. Ethical approval was obtained from the Beijing Cancer Hospital Research Ethics Committee, and every patient signed informed consents before the study.

Study endpoints

The primary objective of this study was to investigate the disease control rate (DCR) and PFS of patients treated with CA (chemotherapy combined with antiangiogenic drugs) regimens after progression on PD-1 inhibitors. The tumor response was evaluated by radiological examinations according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. The DCR was defined as the sum of the percentage of subjects whose best response were complete response (CR), partial response (PR) or stable disease (SD). PFS was defined as the time from the start of the regimen until the date of disease progression, death or last documented contact (censored).

The baseline clinicopathological variables included in our analysis were age (≤65 vs >65 years), sex, Eastern Cooperative Oncology Group (ECOG) score (0 vs ≥1), melanoma subtype, metastatic site, pretreatment neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and lactic dehydrogenase (LDH) level in the peripheral blood, BRAF mutation status, and timing of PD-1 inhibitor treatment (first-line vs second-line or later).

We also explored the association between the efficacy factors of PD-1 inhibitors and the outcomes of CA regimens, including the best response to PD-1 inhibitors, PFS time of anti-PD-1 therapy (p-PFS) (≤3 months vs >3 months), and patterns of PD-1 inhibitor progression (homogeneous vs heterogeneous). Similar to a previous study [15,16], homogeneous progression was defined as an increase of ≥20% in the long axes of each lesion and heterogeneous progression was defined as an increase of ≥20% in the sum of the long axis of all lesions, but not every individual lesion. Additionally, we also analyzed the efficacy of different CA regimens (nab-p plus endostatin vs TMZ combined with apatinib).

Statistical analysis

For statistical convenience, continuous variables were divided into subgroups. We used X-tile software (http://medicine.yale.edu/lab/rimm/research/) to determine the cutoff values for the NLR and PLR based on the minimum *P* values from the log-rank chi-square statistics [17]. The NLR was categorized as<3.5 or ≥3.5, and the PLR was categorized as<200 or ≥200. The chi-square test or Fisher's exact test was used for intergroup comparisons. Univariate and multivariate logistic regression analyses were performed to determine the potential factors associated with the DCR on the CA regimen (c-DCR). The factors associated with c-PFS were analyzed using univariate and multivariate Cox regression analyses. The Kaplan-Meier method was used to describe the prognostic effects of the factors on survival, and survival curves were compared using the log-rank test. All analyses were performed using SPSS (Version 22.0; IBM Corporation, Armonk, NY, USA). A p value of less than 0.05 was considered statistically significant.

Based on the multivariate analysis results, a nomogram was constructed to predict 3-month and 6-month c-PFS probabilities using the RMS package in R version 3.4.4 [18]. The maximum score for each factor was defined as 100. The C-index was utilized to measure the performance of the nomogram.

Results

Patients' baseline clinicopathological characteristics

A total of 69 patients treated at our center were included in accordance with the inclusion criteria. The median age was 53 years (range 21–74 years). All patients were Asian and had stage IV disease. The baseline characteristics are described in Table 1. The majority of the patients were<65 years (88.41%), female (60.87%), had ECOG scores ≥ 1 (65.22%) and had wild-type BRAF (91.30%). In terms of subtypes, 23 (33.33%) patients had cutaneous melanoma, 23 (33.33%) had acral melanoma, 12 (17.39%) had mucosal melanoma, and 11 (15.94%) had unknown primary sites.

At the time of PD-1 inhibitor progression, 33 (47.83%) patients had LDH levels greater than the upper limit of normal (ULN), 20 (28.99%) patients had PLR ≥200, and 28 (40.58%) patients had NLR ≥3.5. The most common metastatic organs were the lungs (32, 46.38%) and the liver (14, 20.29%).

The response and survival of PD-1 inhibitors

All the patients had received PD-1 inhibitors therapy. The median PFS of initial PD-1 inhibitors treatment was 4.2 months (95% CI 3.3–5.1 months), 21 (30.43%) patients received PD-1 inhibitors as first-line therapy, and the remaining 48 (69.57%) patients had received prior treatment before PD-1 inhibitors. As for the response status, 8 patients (11.59%) demonstrated PR, 25 (36.23%) maintained SD, and 37 (53.62%) had progressive disease. Regarding the progression pattern, the majority of patients (54 patients, 78.26%) had homogeneous progression (Table 2).

The response and survival of subsequent CA

All patients received CA therapy after PD-1 inhibitors progression. The median c-PFS time was 3.0 months. Patients received either nab-p plus endostatin ($n = 25$) or TMZ combined with apatinib ($n = 44$). Four patients (5.8%) demonstrated PR, 40 (58.0%) maintained SD, and 25 (36.2%) had progressive disease. The c-DCR was 63.8% and the objective response rate (ORR) was 10%. The median c-PFS time was 3.0 months (95% CI 2.4–3.6).

Table 1
Patient baseline characteristics.

Variable	$N = 69$(%)
Gender, N(%)	
Female	42(60.87)
Male	27(39.13)
Median age(range), year	53(21–74)
Age<65 years, N(%)	
Yes	61(88.41)
No	8(11.59)
Subtype, N(%)	
Cutaneous	23(33.33)
Acral	23(33.33)
Mucosa	12(17.39)
unknown	11(15.94)
ECOG performance status, N(%)	
0	24(34.78)
≥1	45(65.22)
LDH, N(%)	
>ULN	33(47.83)
ULN	36(52.17)
Liver metastases, N(%)	
Yes	14(20.29)
No	55(79.71)
Lung metastases, N(%)	
Yes	32(46.38)
No	37(53.62)
BRAF mutation, N(%)	
Wild type	63(91.30)
Mutant	6(8.70))
Line of PD-1 inhibitor	
First line	21(30.43)
Second-line or more	48(69.57)
Baseline PLR, N(%)	
<200	49(71.01)
≥200	20(28.99)
Baseline NLR, N(%)	
<3.5	41(59.42)
≥3.5	28(40.58)

ECOG, Eastern Cooperative Oncology Group; ULN, upper limit of normal.; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio.

Table 2
Treatment outcome and progression pattern of PD-1 inhibitor[a].

Variable	N (%)
The best response of PD-1 inhibitor	
Progressive disease	37(53.62)
SD	25(36.23)
PR	8(11.59)
PFS of PD-1 inhibitor	
≤3 months	18(26.09)
>3 months	51(73.91)
Progression pattern of PD-1 inhibitor	
homogeneous	54(78.26)
heterogeneous	15(21.74)

SD, stable disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid.
Tumors.
[a] Based on RECIST v1.1.

Univariate and multivariate logistic regression analyses of c-DCR

In terms of the c-DCR, the univariate analysis demonstrated that the cutaneous subtype, baseline PLR and best response to PD-1 inhibitors treatment significantly influenced the prognosis. These prognostic factors were entered into a logistic model for multivariate analysis. The following three factors were considered independent prognostic factors for the c-DCR: cutaneous subtype ($P = 0.011$), baseline PLR≥200 ($P = 0.029$) and nonprogressive disease as the best response to PD-1 inhibitors ($P = 0.003$) (Table 3).

Univariate and multivariate Cox regression analyses of c-PFS

In terms of the c-PFS, the univariate analysis demonstrated that age, baseline LDH, PLR and NLR, best response to PD-1 inhibitor treatment, p-PFS, and progression pattern significantly influenced the prognosis (all $P < 0.05$). These prognostic factors were entered into a Cox model for multivariate analysis. The following three factors were considered independent prognostic factors for c-PFS: age<65 ($P = 0.013$), baseline PLR ≥200 ($P = 0.018$) and heterogeneous progression pattern ($P = 0.012$) (Table 4).

The relationship between the CA regimen and outcomes

No significant differences in the c-DCR ($P = 0.312$) or c-PFS ($P = 0.519$) were observed between the TMZ and nab-p groups. Specific information is displayed in Table 5. We further compared the clinical outcomes of the patients whose p-PFS≤3 months with those whose p-PFS>3 months. In the subgroup including patients with p-PFS≤3 months, nab-p plus endostatin significantly improved c-PFS compared with TMZ combined with apatinib (3.5 vs 2 months, respectively, $P = 0.011$). In the subgroup including patients with p-PFS>3 months, no significant difference was observed.

Construction and validation of the prognostic prediction nomogram for c-PFS

A nomogram was formulated using the independent prognostic factors identified by the Cox proportional hazards model, including age, progression pattern and baseline PLR (Fig. 1). This visual predictive tool can be used to easily obtain the probabilities of the 3-month and 6-month c-PFS of patients. First, each independent prognostic factor was segregated into two levels to correspond to scores based on the point scale at the top of the nomogram. Then, the sum of the points was calculated for each patient to obtain the 3-month and 6-month c-PFS probability corresponding to the bottom point scale of the nomogram. The model demonstrated good accuracy with a C-index of 0.65 (95% CI 0.566–0.734).

According to the median of the nomogram-predicted score, the patients were divided into two cohorts: cohort A (46 cases) and cohort B (23 cases). Survival curves stratified by the nomogram-predicted scores are shown in Fig. 2. Patients with low nomogram-predicted scores exhibited significantly worse survival than those with high nomogram-predicted scores (c-PFS: 1.5 vs 4.0 months; $P < 0.001$).

Discussion

Checkpoint blockade immunotherapy, especially PD-1 inhibitors therapy, has been shown to produce dramatic and durable responses in metastatic melanoma, which has led to approval by the Food and Drug Administration (FDA) in the past few years. Previous studies have confirmed that Chinese melanoma patients have a worse response to PD-1 inhibitor therapy than Caucasians. In our study, the median PFS duration of patients treated with PD-1 inhibitors was 4.2 months, which was shorter than the PFS duration reported in previous clinical trials conducted in other races. Because of the low mutation rate of BRAF in Chinese melanoma patients [19], BRAF inhibitors have limitations in therapeutic application. In our cohort, only 6 patients carried BRAF mutants, which makes the follow-up therapy more difficult.

Current work supports that resistance to PD-1 inhibitors is related to changes in the TME [20]. Chemotherapy can stimulate anti-tumor immunity by inducing immunogenic cell death to enhance antigen presentation [21] and modulate immunosuppressive cells within the TME [22]. Additionally, normalization of the abnormal tumor vasculature induced by antiangiogenic therapy can increase the infiltration of effector immune cells into tumors and convert the intrinsically immunosuppressive TME into an immune supportive TME [23]. Thus, the combination

Table 3
Univariable and multivariable logistic regression for analyzing the associated factors for c-DCR.

Variable	c-DCR					
	Univariate			Multivariate		
	OR	95% CI	P value	OR	95% CI	*P* value
Male	0.944	0.346–2.578	0.911			
Age<65	3.417	0.761–15.746	0.115			
Cutaneous subtype	4.949	1.686–14.533	0.004	0.194	0.055–0.687	0.011
ECOG≥1	1.087	0.389–3.038	0.873			
LDH>ULN	0.597	0.222–1.607	0.307			
Liver metastases	0.486	0.148–1.598	0.235			
Lung metastases	0.544	0.202–1.467	0.229			
BRAF mutation	3.077	0.339–27.948	0.318			
Baseline PLR≥200	0.178	0.048–0.661	0.011	0.233	0.063–0.861	0.029
Baseline NLR≥3.5	0.367	0.133–1.010	0.052			
Line of PD-1>1	1.5	0.524–4.296	0.45			
Non-PD (PD-1 response)	6.353	2.006–20.117	0.002	7.58	2.016–28.51	0.003
P-PFS>3 months	3	0.991–9.083	0.052			
Heterogeneous progression	2.75	0.694–10.895	0.15			
Nab-p/endostatin	0.594	0.216–1.636	0.313			

c-DCR, disease control rate of salvage regimen; OR, odds ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ULN, upper limit of normal; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PD, progressive disease; P-PFS, progression-free survival of PD-1 inhibitor; nab-p, nab-paclitaxel. All P values were two-tailed.

Table 4
Univariate and multivariate Cox regression analyses estimating the risk factors for c-PFS.

Variable	c-PFS					
	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	*P* value
Male	0.876	0.498–1.541	0.647			
Age<65	0.35	0.163–0.754	0.007	0.364	0.165–0.806	0.013
Cutaneous subtype	1.669	0.946–2.942	0.077			
ECOG≥1	1.309	0.715–2.394	0.383			
LDH>ULN	1.769	1.013–3.091	0.045			0.225
Liver metastases	1.533	0.816–2.877	0.184			
Lung metastases	1.045	0.607–1.799	0.873			
BRAF mutation	0.895	0.355–2.252	0.813			
Baseline PLR≥200	2.245	1.263–3.990	0.006	2.011	1.125–3.596	0.018
Baseline NLR≥3.5	1.888	1.080–3.302	0.026			0.933
Line of PD1>1	1.22	0.678–2.197	0.507			
Non-PD(PD-1 response)	0.553	0.318–0.962	0.036			0.191
P-PFS>3 months	0.474	0.262–0.859	0.014			0.196
Heterogeneous progression	0.424	0.201–0.895	0.024	0.38	0.179–0.807	0.012
Nab-p/endostatin	1.041	0.593–1.826	0.889			

c-PFS, progression-free survival of salvage regimen; HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ULN, upper limit of normal; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PD, progressive disease; P-PFS, progression-free survival of PD-1 inhibitor; nab-p, nab-paclitaxel. All *P* values were two-tailed.

Table 5
Summary of responses data for different CA regimens.

Variable	nab-p/endostatin $n=25$	TMZ/apatinib $n=49$	*P* value
Progressive disease (n)	11	14	–
SD (n)	13	27	–
PR (n)	1	3	–
Disease control rate	56.00%	68.18%	0.312
Objective response rate	3.84%	6.82%	1.000
Median PFS (95%CI) (months)	3.000 (2.259–3.741)	3.000 (0.935–5.065)	0.887

CA: chemotherapy combined with antiangiogenic drugs; SD: stable disease; PR: partial response; PFS: progression-free survival; nab-p: nab-paclitaxel; TMZ: temozolomide; CI, confidence interval; All P values were two-tailed.

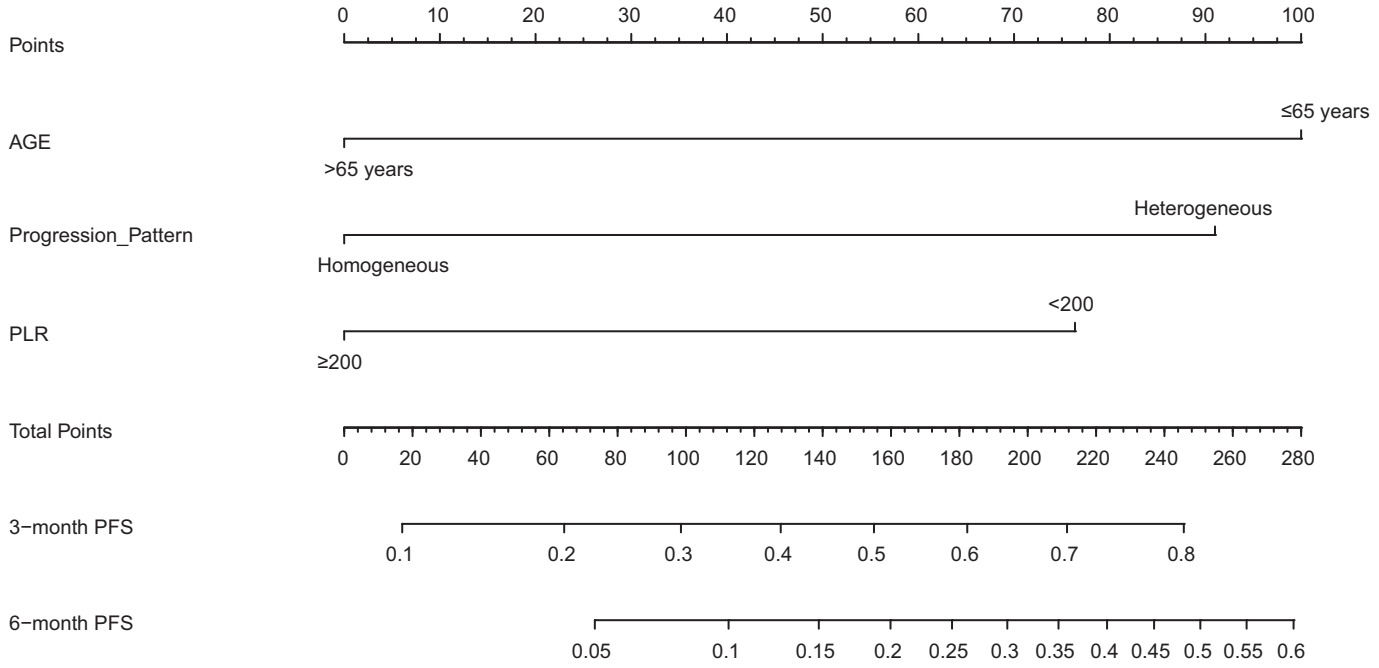

Fig. 1. Nomogram predicting c-PFS in our cohort. The nomogram to predict c-PFS was created based on three independent prognostic factors. Abbreviations: c-PFS, progression-free survival of salvage regimen; PLR, platelet-to-lymphocyte ratio.

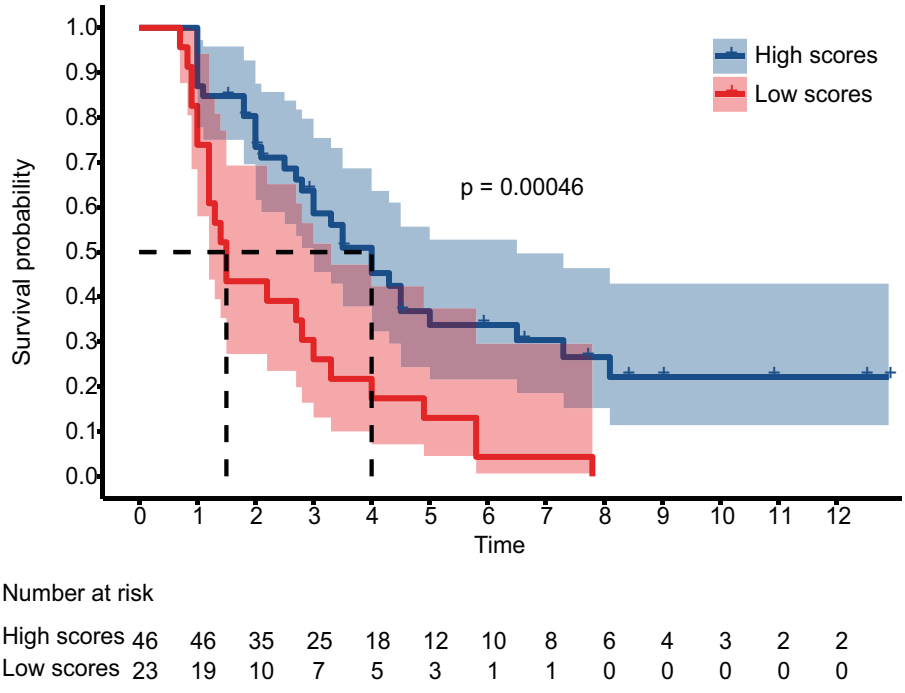

Fig. 2. Kaplan-Meier curves demonstrating c-PFS in the subgroups according to the total score of the nomogram. Abbreviations: c-PFS, progression-free survival of salvage regimen.

Number at risk

High scores	46	46	35	25	18	12	10	8	6	4	3	2	2
Low scores	23	19	10	7	5	3	1	1	0	0	0	0	0

of chemotherapy with antiangiogenic therapy may theoretically have synergistic anti-tumor effects.

Previous studies have confirmed the efficacy and safety of TMZ combined with apatinib in Chinese melanoma patients [12]. These two drugs are given orally which makes this CA regimen easy to administer and well accepted by patients. Besides, nab-p plus endostatin is another commonly used CA regimen in our clinical practice. This retrospective study was the first to evaluate this treatment strategy in melanoma patients who progressed after PD-1 inhibitors treatment. In our research, the c-DCR was 63.8%, and the median c-PFS time was 3.0 months, which indicated a promising therapeutic effect.

We explored whether different CA regimens would impact c-PFS. In the whole population, we did not find significant differences in c-PFS between the different regimens. However, in the subgroup of patients with p-PFS ≤ 3 months, nab-p plus endostatin significantly improved c-PFS compared with TMZ combined with apatinib. Paclitaxel has been shown to contribute to macrophage activation [24] and then exert a positive effect on T cell proliferation [25]. It can also reduce the numbers of immunosuppressive cells, such as regulatory T cells (Tregs) [26,27], and drive the production of immunoenhancing cytokines, including IL-12, IFNγ, TNFα and granulocyte-macrophage colony-stimulating factor (GM-CSF) [21]. Recent data demonstrated that a combination therapy

consisting of nab-p with a PD-1 inhibitor could overcome the resistance to PD-1 inhibitors in pancreatic cancer [28]. It is possible that the immune supportive function of anti-PD-1 treatment is still present at the time of chemotherapy administration and that nab-p can help reactivate the immune response and augment anti-tumor activity.

The associations between the treatment effects of CA and clinicopathological features were investigated. Patients with the cutaneous melanoma subtype generally have a good prognosis, which has been demonstrated in Asian patients [29]. However, we found a lower c-DCR for the cutaneous subtype than for other subtypes. The underlying reason is unclear and needs to be further investigated.

Assays of the NLR and PLR are standardized tests and can be highly cost-effective. In recent years, high NLR and PLR values have been considered poor predictive markers in patients with solid tumors. We found that high PLR after PD-1 inhibitor progression was associated with poor c-DCR and c-PFS, which was consistent with previous studies [30-33]. Although no significant difference was found in the multivariate analysis, the same trend was observed for the NLR. Both the NLR and PLR are considered to reflect the inflammatory response through a mechanism by which cytokine and chemokine release induces immune infiltration into tumor lesions and triggers inflammatory progression [34,35]. High PLR is considered to be caused by thrombopoiesis cytokines such as interleukin-6 (IL-6) secreted by tumor cells [36]. In vivo angiogenic assays showed that IL-6 could increase the angiogenic activity of tumor cells, an effect that is specifically associated with the upregulation of VEGF. Additionally, using an anti-VEGF antibody to block VEGF function can significantly inhibit IL-6-mediated angiogenesis and tumor growth in nude mice [37]. However, in our study, even with antiangiogenic drug treatments, patients with high PLR still had worse outcomes, which indicated that the addition of VEGF inhibitors was not sufficient to reverse a poor prognosis. Thus, new treatment drugs, such as an anti-IL-6 antibody, need to be further explored.

We also explored the relationship between the progression patterns after previous PD-1 inhibitor therapy and the effects of CA regimens. As in many other studies [15,16], we defined different patterns of PD-1 progression (homogeneous vs heterogeneous) and found that heterogeneous progression was associated with prolonged c-PFS. This may have occurred because PD-1 inhibitors exhibited definite curative effects in most patients demonstrating the lasting clinical benefits that can be effective for an extended period of time to improve the curative effect of CA regimens. The possible mechanism may be that CA regimens can promote tumor antigen release and, increase antigen expression, leading to normalization of the TME and reactivation of the immune system, thus resulting in survival benefits [23,38]. Further studies and appropriate clinical trials, such as PD-1 inhibitors treatments combined with CA, will be required to test this hypothesis.

Based on the multivariate analysis results, we developed a prognostic model to predict 3- and 6-month c-PFS probabilities. To our knowledge, this is the first study to attempt to establish a prognostic nomogram for these advanced melanoma patients. We concluded that age, progression pattern and baseline PLR were independent prognostic factors for c-PFS. The nomogram presented good discriminative ability, with a C-index of 0.65 (95% CI 0.566–0.734).

The limitations of this study include a relatively small sample size, differences in the baseline status of patients, the short observation period which led to a deficiency in overall survival (OS) data, and the lack of external validation of the nomogram. Appropriate clinical trials are needed to further explore the treatment effects of CA regimens, and large-scale data are required to confirm the efficacy of the nomogram in the future.

Conclusion

Our study, for the first time, reported the efficacy of treatment with nab-p or TMZ combined with an antiangiogenic drug after the development of resistance to PD-1 inhibitors in Asian melanoma patients. The results showed that CA regimens have a promising treatment effect on patients with PD-1 inhibitor resistance. Age <65 years, heterogeneous progression pattern and baseline PLR <200 were significantly associated with improved c-PFS. A nomogram including these factors could be a valuable predictive module for salvage therapy selection in PD-1 inhibitor-resistant patients.

Declaration of Competing Interest

None

CRediT authorship contribution statement

Zhihong Chi: Methodology. **Lu Si:** Supervision. **Xinan Sheng:** Visualization. **Yan Kong:** Software. **Li Zhou:** Validation. **Lili Mao:** Formal analysis. **Bin Lian:** Resources. **Bixia Tang:** Project administration. **Xieqiao Yan:** Data curation. **Xue Bai:** Data curation.

Funding

This study was supported by the Peking University Cancer Hospital Special Fund for Clinical Research.

References

[1] J.J. Luke, K.T. Flaherty, A. Ribas, G.V Long, Targeted agents and immunotherapies: optimizing outcomes in melanoma, Nat. Rev. Clin. Oncol. 14 (8) (2017) 463–482.
[2] C. Robert, G.V. Long, B. Brady, C. Dutriaux, M. Maio, L. Mortier, et al., Nivolumab in previously untreated melanoma without BRAF mutation, N. Engl. J. Med. 372 (4) (2015) 320–330.
[3] J.S. Weber, G. Gibney, R.J. Sullivan, J.A. Sosman, C.L. Slingluff Jr., D.P. Lawrence, et al., Sequential administration of nivolumab and ipilimumab with a planned switch in patients with advanced melanoma (CheckMate 064): an open-label, randomised, phase 2 trial, Lancet Oncol. 17 (7) (2016) 943–955.
[4] P. Sharma, S. Hu-Lieskovan, J.A. Wargo, A Ribas, Primary, adaptive, and acquired resistance to cancer immunotherapy, Cell 168 (4) (2017) 707–723.
[5] P. Salven, P. Heikkila, H Joensuu, Enhanced expression of vascular endothelial growth factor in metastatic melanoma, Br. J. Cancer 76 (7) (1997) 930–934.
[6] S. Ugurel, G. Rappl, W. Tilgen, U Reinhold, Increased serum concentration of angiogenic factors in malignant melanoma patients correlates with tumor progression and survival, J. Clin. Oncol. 19 (2) (2001) 577–583.
[7] Y. Huang, J. Yuan, E. Righi, W.S. Kamoun, M. Ancukiewicz, J. Nezivar, et al., Vascular normalizing doses of antiangiogenic treatment reprogram the immunosuppressive tumor microenvironment and enhance immunotherapy, Proc. Natl. Acad. Sci. 109 (43) (2012) 17561–17566.
[8] L. Xie, W. Guo, Y. Wang, T. Yan, T. Ji, J Xu, Apatinib for advanced sarcoma: results from multiple institutions' off-label use in China, BMC Cancer 18 (1) (2018) 396.
[9] C. Yang, W. Feng, D Wu, Apatinib for advanced nonsmall-cell lung cancer: a retrospective case series analysis, J. Cancer Res. Ther. 14 (1) (2018) 159.
[10] M.S. O'Reilly, L. Holmgren, Y. Shing, C. Chen, R.A. Rosenthal, M. Moses, et al., Angiostatin: a novel angiogenesis inhibitor that mediates the suppression of metastases by a Lewis lung carcinoma, Cell 79 (2) (1994) 315–328.
[11] C. Cui, L. Mao, Z. Chi, L. Si, X. Sheng, Y. Kong, et al., A phase II, randomized, double-blind, placebo-controlled multicenter trial of Endostar in patients with metastatic melanoma, Mol. Ther. 21 (7) (2013) 1456–1463.
[12] C. Cui, L. Zhou, B. Lian, L. Si, X. Sheng, Z. Chi, et al., Safety and efficacy of apatinib combined with temozolomide in advanced melanoma patients after conventional treatment failure, Transl. Oncol. 11 (5) (2018) 1155–1159.
[13] E.M. Hersh, S.J. O'Day, A. Ribas, W.E. Samlowski, M.S. Gordon, D.E. Shechter, et al., A phase 2 clinical trial of nab-paclitaxel in previously treated and chemotherapy–naive patients with metastatic melanoma, Cancer 116 (1) (2010) 155–163.
[14] E.M. Hersh, M. Del Vecchio, M.P. Brown, R. Kefford, C. Loquai, A. Testori, et al., A randomized, controlled phase III trial of nab-Paclitaxel versus dacarbazine in chemotherapy-naive patients with metastatic melanoma, Ann. Oncol. 26 (11) (2015) 2267–2274.
[15] I. Pires da Silva, S. Lo, C. Quek, M. Gonzalez, M.S. Carlino, G.V. Long, et al., Site-specific response patterns, pseudoprogression, and acquired resistance in patients with melanoma treated with ipilimumab combined with anti–PD-1 therapy, Cancer 126 (1) (2020) 86–97.
[16] J.H. Lee, M. Lyle, A.M. Menzies, M.M. Chan, S. Lo, A. Clements, et al., Metastasis-specific patterns of response and progression with anti-PD-1 treatment in metastatic melanoma, Pigment Cell Melanoma Res. 31 (3) (2018) 404–410.
[17] R.L. Camp, M. Dolled-Filhart, D.L Rimm, X-tile: a new bio-informatics tool for biomarker assessment and outcome-based cut-point optimization, Clin. Cancer Res. 10 (21) (2004) 7252–7259.
[18] E.H.J. F. Rms: Regression Modeling Strategies. R Package version 3.4-4. Available from: http://www.rprojectorg/. October 17, 2018.
[19] L. Si, Y. Kong, X. Xu, K.T. Flaherty, X. Sheng, C. Cui, et al., Prevalence of BRAF V600E mutation in Chinese melanoma patients: large scale analysis of BRAF and NRAS mutations in a 432-case cohort, Eur. J. Cancer 48 (1) (2012) 94–100.

[20] J.M. Pitt, M. Vétizou, R. Daillère, M.P. Roberti, T. Yamazaki, B. Routy, et al., Resistance mechanisms to immune-checkpoint blockade in cancer: tumor-intrinsic and-extrinsic factors, Immunity 44 (6) (2016) 1255–1269.
[21] G. Kroemer, L. Galluzzi, O. Kepp, L Zitvogel, Immunogenic cell death in cancer therapy, Annu. Rev. Immunol. 31 (2013) 51–72.
[22] K. Kim, A.D. Skora, Z. Li, Q. Liu, A.J. Tam, R.L. Blosser, et al., Eradication of metastatic mouse cancers resistant to immune checkpoint blockade by suppression of myeloid-derived cells, Proc. Natl. Acad. Sci. 111 (32) (2014) 11774–11779.
[23] D. Fukumura, J. Kloepper, Z. Amoozgar, D.G. Duda, R.K Jain, Enhancing cancer immunotherapy using antiangiogenics: opportunities and challenges, Nat. Rev. Clin. Oncol. 15 (5) (2018) 325–340.
[24] J. Cullis, D. Siolas, A. Avanzi, S. Barui, A. Maitra, D Bar-Sagi, Macropinocytosis of nab-paclitaxel drives macrophage activation in pancreatic cancer, Cancer Immunol. Res. 5 (3) (2017) 182–190.
[25] W.E. Carson, C.L. Shapiro, T.R. Crespin, L.M. Thornton, B.L Andersen, Cellular immunity in breast cancer patients completing taxane treatment, Clin. Cancer Res. 10 (10) (2004) 3401–3409.
[26] N. Tsuda, D.Z. Chang, T. Mine, C. Efferson, A. García-Sastre, X. Wang, et al., Taxol increases the amount and T cell–activating ability of self-immune stimulatory multimolecular complexes found in ovarian cancer cells, Cancer Res. 67 (17) (2007) 8378–8387.
[27] A.P. Vicari, R. Luu, N. Zhang, S. Patel, S.R. Makinen, D.C. Hanson, et al., Paclitaxel reduces regulatory T cell numbers and inhibitory function and enhances the anti-tumor effects of the TLR9 agonist PF-3512676 in the mouse, Cancer Immunol. Immunother. 58 (4) (2009) 615–628.
[28] G.J. Weiss, L. Blaydorn, J. Beck, K. Bornemann-Kolatzki, H. Urnovitz, E. Schütz, et al., Phase Ib/II study of gemcitabine, nab-paclitaxel, and pembrolizumab in metastatic pancreatic adenocarcinoma, Invest. New Drugs 36 (1) (2018) 96–102.
[29] Z. Chi, S. Li, X. Sheng, L. Si, C. Cui, M. Han, et al., Clinical presentation, histology, and prognoses of malignant melanoma in ethnic Chinese: a study of 522 consecutive cases, BMC Cancer 11 (1) (2011) 85.
[30] F. Wang, Z.-.Y. Liu, Y.-.Y. Xia, C. Zhou, X.-.M. Shen, X.-.L. Li, et al., Changes in neutrophil/lymphocyte and platelet/lymphocyte ratios after chemotherapy correlate with chemotherapy response and prediction of prognosis in patients with unresectable gastric cancer, Oncol. Lett. 10 (6) (2015) 3411–3418.
[31] Y. Miao, Q. Yan, S. Li, B. Li, Y Feng, Neutrophil to lymphocyte ratio and platelet to lymphocyte ratio are predictive of chemotherapeutic response and prognosis in epithelial ovarian cancer patients treated with platinum-based chemotherapy, Cancer Biomark 17 (1) (2016) 33–40.
[32] Y. Wu, C. Li, J. Zhao, L. Yang, F. Liu, H. Zheng, et al., Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios predict chemotherapy outcomes and prognosis in patients with colorectal cancer and synchronous liver metastasis, World J. Surg. Oncol. 14 (1) (2016) 289.
[33] Y. Ding, S. Zhang, J Qiao, Prognostic value of neutrophil-to-lymphocyte ratio in melanoma: evidence from a PRISMA-compliant meta-analysis, Medicine (Baltimore) 97 (30) (2018).
[34] C. Jenne, R. Urrutia, P Kubes, Platelets: bridging hemostasis, inflammation, and immunity, Int. J. Lab Hematol. 35 (3) (2013) 254–261.
[35] G.J. Guthrie, K.A. Charles, C.S. Roxburgh, P.G. Horgan, D.C. McMillan, S.J Clarke, The systemic inflammation-based neutrophil–lymphocyte ratio: experience in patients with cancer, Crit. Rev. Oncol. Hematol. 88 (1) (2013) 218–230.
[36] D. Buergy, F. Wenz, C. Groden, M.A Brockmann, Tumor–platelet interaction in solid tumors, Int. J. Cancer 130 (12) (2012) 2747–2760.
[37] L-H Wei, M.-.L. Kuo, C.-.A. Chen, C.-.H. Chou, K.-.B. Lai, C.-.N. Lee, et al., Interleukin-6 promotes cervical tumor growth by VEGF-dependent angiogenesis via a STAT3 pathway, Oncogene 22 (10) (2003) 1517–1527.
[38] M. Hong, A.L. Puaux, C. Huang, L. Loumagne, C. Tow, C. Mackay, et al., Chemotherapy induces intratumoral expression of chemokines in cutaneous melanoma, favoring T-cell infiltration and tumor control, Cancer Res. 71 (22) (2011) 6997–7009.