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ORIGINAL ARTICLE

Safety of shortened infusion times for combined ipilimumab and nivolumab

Maximilian Gassenmaier[1] · Hans-Peter Lipp[2] · Alexander Scheu[1] · Nikolaus Benjamin Wagner[1] · Lukas Kofler[1] · Alisa Mueller[1] · Dennis Doecker[1] · Thomas Kurt Eigentler[1] · Claus Garbe[1] · Andrea Forschner[1]

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Abstract
Background Combined ipilimumab and nivolumab induces encouraging response rates in patients with unresectable or metastatic melanoma. However, the approved protocol for dual checkpoint inhibition (3 mg/kg ipilimumab over 90 min and 1 mg/kg nivolumab over 60 min) is time-intensive and several trials have shown that both single agents can be safely administered at faster infusion rates.
Aim To investigate whether combined checkpoint inhibition with 3 mg/kg ipilimumab and 1 mg/kg nivolumab can be safely administered over 30 min per agent.
Patients and methods We reviewed the rate of infusion-related reactions (IRRs) in the first 12 months of our single-institution experience using shortened infusion times for combined checkpoint inhibition with ipilimumab and nivolumab.
Results Between May 24, 2016 and June 10, 2017, a total of 46 melanoma patients received 100 shortened cycles of combined 3 mg/kg ipilimumab and 1 mg/kg nivolumab. One patient (2.2%; 1/46) had a questionable reaction after administration of 1 mg/kg nivolumab over 30 min, but none of the other patients had a bona fide IRR.
Conclusions Shortened infusion times for combined ipilimumab and nivolumab treatment are safe, thereby facilitating a more efficient use of outpatient facilities and enhancing patient's convenience.

✉ Andrea Forschner
andrea.forschner@med.uni-tuebingen.de

[1] Department of Dermatology, Center for Dermatooncology, Eberhard-Karls-University of Tuebingen, Tübingen, Germany

[2] Department of Clinical Pharmacy, Eberhard-Karls-University of Tuebingen, Tübingen, Germany

Keywords Melanoma · Immunotherapy · Ipilimumab · Nivolumab · Infusion rate · Infusion-related reaction

Abbreviations

AJCC	American Joint Committee on Cancer
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte antigen-4
ECOG	Eastern Cooperative Oncology Group
IQR	Interquartile range
irAEs	Immune-related adverse events
IRR	Infusion-related reaction
mAb	Monoclonal antibody
NA	Not available
PD-1	Programmed cell death protein 1

Introduction

Ipilimumab and nivolumab were approved by the US Food and Drug Administration in October 2015 and by the European Medicines Agency in May 2016 as first and only immuno-oncology combination for the treatment of patients with unresectable or metastatic melanoma. Both agents are fully human monoclonal antibodies (mAbs) targeting T cell coinhibitory markers. Ipilimumab is directed against the cytotoxic T-lymphocyte antigen-4 (CTLA-4) and nivolumab against the programmed cell death protein 1 (PD-1). Clinical trials showed objective response rates of about 60% for combination of CTLA-4 and PD-1 blockade with longer progression-free survival and higher objective response rate than either agent alone [1–3].

The approved dose and schedule of combined immune checkpoint inhibition is intravenous infusion of 1 mg/kg nivolumab over 60 min plus 3 mg/kg ipilimumab over

90 min every 3 weeks for up to four cycles, followed by 3 mg/kg nivolumab over 60 min every 2 weeks thereafter as monotherapy.

The rationale for the low infusion rate has not yet been elucidated in detail, but it presumably intends to minimize the incidence of IRRs [4]. However, faster infusion protocols have been successfully established, such as 3 mg/kg ipilimumab over 30 min [4] and 10 mg/kg over 90 min [5]. Moreover, 1 mg/kg nivolumab is infused in the first 20 min when patients receive 3 mg/kg nivolumab monotherapy over 60 min, suggesting that a 30-min infusion should be safe as well. These considerations led to a change in our institutional infusion guideline because faster infusion of combined immunotherapy would allow a more efficient use of our outpatient facilities and enhance patient convenience.

In this report, we retrospectively reviewed the incidence of IRRs in melanoma patients treated with combined 3 mg/kg ipilimumab and 1 mg/kg nivolumab over 30 min per agent at our institution between May 24, 2016 and June 10, 2017.

Patients and methods

Indication for combined ipilimumab and nivolumab treatment was confirmed by a multidisciplinary tumor board. The following protocol was used for the shortened infusions and approved by the Department of Clinical Pharmacy of the University Hospital Tuebingen: at first, 100 ml of 0.9% normal saline i.v. short-infusion was given to reassure the correct position of the intravenous cannula. Subsequently, 1 mg/kg nivolumab, which has been added to 50 ml of 0.9% normal saline, was administered i.v. over 30 min, followed by 100 ml of 0.9% normal saline i.v. over another 30 min. Thereafter, 3 mg/kg ipilimumab, which has been mixed with 0.9% normal saline to a final volume of 100 ml, was administered i.v. over 30 min, followed by a final 100 ml of 0.9% normal saline i.v. short-infusion. Infusions were administered in direct proximity to the staff of the Center of Dermatooncology and all patients were equipped with bells to call attention in case of discomfort during infusions. Blood pressure was measured at the beginning, after completing nivolumab infusion and at the end of each infusion cycle. All patients were monitored for at least 30 min after completion of combined immunotherapy.

Before each infusion cycle, all patients were seen by dermatologists for completion of standardized checklists to record the current ECOG (Eastern Cooperative Oncology Group) performance status, body weight, presence of B symptoms (fever, night sweats, weight loss) and to rule out any immune-related adverse events (irAEs). If patients were on systemic steroids for treatment of irAEs, immunotherapy was continued at a dose of 10 mg or less prednisone equivalent daily. Treatment was only given if up-to-date blood exam (complete blood count, liver and kidney function tests, electrolytes, amylase, lipase, creatine kinase, blood glucose, lactate dehydrogenase, S100B, thyroid-stimulating hormone and free triiodothyronine/free thyroxine) and urinalysis were checked. Exclusion criteria for shortened immunotherapy infusions were uncontrolled or symptomatic brain metastasis, glomerular filtration rate of less than 30 ml/min/1.73 m^2 and ECOG performance status more than 2. The change in infusion times was done as a clinical decision and outcomes were reviewed retrospectively based on computerized medical records.

Statistical calculations were performed with IBM SPSS Statistics Version 23.0 (IBM SPSS, Chicago, Illinois, USA). Skewed numerical variables were described by median value and interquartile range (IQR). The incidence of IRRs among fast and slow infusion rates was compared with Pearson's χ^2 test and Fisher's exact test, respectively. Throughout the analysis, p values less than 0.05 were considered as statistically significant.

Results

Between May 24, 2016 and June, 10, 2017, 46 patients received a total of 131 cycles combined immunotherapy according to either the standard ($n = 31$) or the shortened infusion protocol ($n = 100$). Patient and treatment characteristics are summarized in Table 1. Treatment was discontinued due to progression ($n = 5$, 10.9%), irAEs ($n = 5$, 10.9%; colitis $n = 3$, 6.5%; nephritis $n = 1$, 2.2%; meningoencephalitis $n = 1$, 2.2%) or death ($n = 1$, 2.2%). Three patients (6.5%) were lost to follow up and 18 patients (39.1%) were still on treatment at the time of this report.

One patient (2.2%; 1/46) had an episode of syncope during the shortened infusion cycle that might be associated with the shortened infusion protocol (see "Case report").

Case report

An 82-year-old female patient with known carotid artery disease and newly diagnosed stage IV melanoma of unknown primary was started on combined immunotherapy with ipilimumab and nivolumab and tolerated cycle 1 without incident. At presentation for the second cycle, she reported a new onset of vertigo and nausea. Blood pressure was 100/70 mmHg at the beginning of the infusion. After completion of the nivolumab dose, the patient suffered a sudden loss of consciousness and was responsive again shortly after. Blood pressure was 150/80 mmHg and electrocardiogram showed no signs of arrhythmia or ischemia. Troponin I was normal at baseline and 4 h later. Symptoms

Table 1 Patient and treatment characteristics

	No. of patients (% of total)
Gender	
Female	24 (52.4%)
Male	22 (47.6%)
Age, years	
Median (IQR)	63 (52–75)
ECOG performance status	
0	34 (73.9%)
1	9 (19.6%)
NA	3 (6.5%)
Melanoma stage at treatment start (AJCC)	
Cutaneous melanoma or melanoma of unknown primary	38 (82.6%)
IIIC	2 (4.3%)
IVM1b	5 (10.9%)
IVM1c	31 (67.4%)
Mucosal melanoma	2 (4.3%)
IV	2 (4.3%)
Uveal melanoma	6 (13.0%)
IV	6 (13.0%)
Brain metastasis at treatment start	
No	44 (95.7%)
Yes	2 (4.3%)
Previous treatments	
None	19 (41.3%)
Adjuvant low-dose interferon alpha	15 (32.6%)
Chemotherapy	4 (8.7%)
Ipilimumab	7 (15.2%)
Anti-PD-1 antibody	18 (39.1%)
BRAF ± MEK inhibitor	5 (10.9%)
Number of total infusion cycles (regular and shortened)	131
1 cycle	8 (17.4%)
2 cycles	9 (19.6%)
3 cycles	11 (23.9%)
4 cycles	18 (39.1%)
Number of shortened infusion cycles	100
1 cycle	20 (43.5%)
2 cycles	8 (17.4%)
3 cycles	8 (17.4%)
4 cycles	10 (21.7%)

resolved spontaneously within minutes and thus, ipilimumab was administered over 90 min. The patient was admitted to the dermatology ward for observation and discharged on the next morning. Two weeks later, the patient suffered a second episode of syncope outside the hospital which was not related to any immunotherapy infusion. Echocardiography showed a normal left ventricular ejection fraction and cardiac workup was negative. Cycles 3 and 4 were infused according to the standard protocol (1 mg/kg nivolumab over 60 min and 3 mg/kg ipilimumab over 90 min) without incident.

Discussion

Infusion regimens of newly approved mAbs commonly include slow infusion rates to minimize the incidence of IRRs. However, it has been shown for numerous antibodies that faster infusion schemes can be applied safely as clinicians have gained more experience with the respective agents [6–8]. In addition, the half-life of most mAbs including ipilimumab and nivolumab with 15.4 and 26.7 days, respectively is rather long [9, 10]. As a consequence, it cannot be expected that a shorter infusion duration may impact efficacy [8].

IRRs to mAbs occur primarily during the first and second exposure to the drug and within a few hours after beginning of the infusion [4, 11, 12]. The majority of IRRs is mild to moderate with symptoms such as fever, shaking chills, nausea, dyspnea, headache, hypo- and hypertension or rash, but a small percentage of patients can develop severe and even fatal reactions [11]. The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) [13] distinguish between acute infusion reactions (cytokine release syndrome) and hypersensitivity reactions (allergic reactions) [11]. The exact mechanisms of mAbs-induced IRRs remain unclear, but some reactions seem to be related to antibody interactions with target cells (e.g. rituximab with CD20), thereby promoting the release of inflammatory cytokines such as tumor necrosis factor alpha and interleukin 6 [14]. The severity of these reactions correlates with the number of target cells [15], the density of antigen expression [16] and infusion rate [17]. However, preclinical safety studies have shown no complement-mediated or antibody-dependent cell-mediated cytotoxicity of nivolumab and ipilimumab on activated T cells [18], and ipilimumab has been reported to even increase the frequency of activated T cells [19].

The incidence of mAb-associated IRRs is further influenced by the extent of antibody humanization, with a higher frequency among chimeric antibodies (77% for rituximab) and lower incidence among humanized (40% for trastuzumab) or fully human mAbs (4% for panitumumab) [14, 20]. True type I hypersensitivity reactions are relatively uncommon upon use of mAbs [12], and less than 2% of all melanoma patients ($n = 767$) receiving ipilimumab in phase 2 and 3 trials developed antibodies against the agent [10]. However, the clinical importance of this finding remains unclear since none of these patients developed infusion-related hypersensitivity reactions or neutralizing antibodies. Furthermore, no correlation between the development of anti-ipilimumab antibodies and incidence of adverse

events was found. A pooled analysis of patients receiving nivolumab monotherapy accounted for 5.4% (108/1991) IRRs including five grade 3 and two grade 4 reactions [9]. A somewhat lower frequency, and exclusively grade 1 or 2 IRRs (3.8%; 17/448) were found among patients with combined ipilimumab and nivolumab treatment [9]. Management of mild to moderate IRRs usually involves temporary infusion interruption, supportive therapy with antihistamines, patient monitoring, and reduction of the infusion rate. Most patients will tolerate subsequent doses with premedication (antihistamines) and slower infusion rates [4, 11].

We reviewed the PubMed database for the reported incidence of IRRs among cancer patients treated with ipilimumab and/or nivolumab in prospective randomized phase 2 and 3 trials using the search terms "ipilimumab OR nivolumab" and restricting the search to the article type "Clinical Trial". We included hypersensitivity reactions since some trials distinguished between IRRs and hypersensitivity reactions and others did not. Data are summarized in Table 2 and suggest that the frequency of IRRs depends on both infusion rate and cancer entity. The highest rate of IRRs (16.0%; 42/263) was found in classical non-Hodgkin lymphoma patients as compared to 2.7% (21/787) IRRs among melanoma patients treated with 3 mg/kg nivolumab over 60 min. A recent phase 3 trial, comparing two dosing schemes of ipilimumab showed a higher frequency of IRRs when 10 mg/kg ipilimumab was administered over 90 min as compared to 3 mg/kg ipilimumab over 90 min [5]. In the 10 mg/kg study arm, 4.1% (15/364) experienced IRR as compared to 0.6% (2/362) of patients in the 3 mg/kg study arm (Pearson's χ^2 test, $p = 0.001$).

Moreover, patients treated with 3 mg/kg ipilimumab over 30 min outside a randomized trial had a somewhat higher rate of IRRs as compared to patients treated with 3 mg/kg over 90 min (5.8% [7/120] vs. 2.2% [10/457]; Fisher's exact test, $p = 0.06$) [4]. All IRRs of the fast infusion protocol developed either within or up to 30 min after the infusion, but none of the IRRs was dose-limiting.

In our study, 46 patients received a total of 100 shortened cycles of combined immunotherapy without any bona fide IRR. One patient (2.2%; 1/46) had a questionable reaction that was most likely unrelated to the shortened infusion protocol, since the patient presented with a new onset of vertigo before the infusion and suffered a second episode of syncope 2 weeks later unassociated with any immunotherapy. Although a clear limitation of this study is the small number of patients, our findings add to the growing body of evidence that faster infusion of checkpoint inhibitors is not associated with an exceeding rate of IRRs. For instance, several clinical trials have demonstrated the safety of infusing 1 mg/kg nivolumab within 20 min since 3 mg/kg is administered within 60 min according to the standard protocol [1, 21–23].

However, the incidence of IRRs is presumably somewhat higher at the faster infusion rate than what has already been shown for ipilimumab monotherapy [4, 5], and has yet to be investigated for combined immunotherapy in large prospective trials.

Moreover, it remains unclear whether the fast infusion protocol can be applied with the same safety profile in patients with uncontrolled brain metastasis, poor ECOG performance status and impaired renal function since these patients were excluded in this study.

On the other hand, the study is strengthened by the highly standardized infusion procedure and close-meshed patient monitoring during infusions, warranting a reliable detection of possible IRRs.

Table 2 Reported frequency of IRRs in randomized prospective trials

Trial	Cancer entity	Year	Agent	Infusion rate	IRR	Grade (CTCAE) [a]	
						1–2	3
CheckMate 069, 067 [1, 3, 23]	Melanoma	2015	Ipilimumab + Nivolumab	3 mg/kg over 90 min 1 mg/kg over 60 min	10/407 (2.5%)	$n = 10$ (2.5%)	–
CheckMate 037, 066, 067 [1, 21–23]	Melanoma	2015	Nivolumab	3 mg/kg over 60 min	21/787 (2.7%)	$n = 19$ (2.4%)	$n = 2$ (0.3%)
NCT01515189 [5]	Melanoma	2017	Ipilimumab	10 mg/kg over 90 min	15/364 (4.1%)	$n = 11$ (3.0%)	$n = 4$ (1.1%)
				3 mg/kg over 90 min	2/362 (0.6%)	$n = 1$ (0.3%)	$n = 1$ (0.3%)
KEYNOTE-006 [24]	Melanoma	2015	Ipilimumab	3 mg/kg over 90 min	2/256 (0.8%)	$n = 2$ (0.8%)	–
CheckMate 057 [23, 25]	Nonsquamous non-small-cell lung cancer	2015	Nivolumab	3 mg/kg over 60 min	9/287 (3.1%)	$n = 9$ (3.1%)	–
CheckMate 025 [23, 26]	Renal cell carcinoma	2015	Nivolumab	3 mg/kg over 60 min	25/406 (6.2%)	NA	
CheckMate 205 and 039 [23]	Classical Hodgkin lymphoma	2016	Nivolumab	3 mg/kg over 60 min	42/263 (16.0%)	$n = 40$ (15.2%)	$n = 2$ (0.8%)

[a]The severity of adverse events was graded according to the CTCAE version 4.0 [13]

In conclusion, this single-institution study and data from prospective trials highlight that both ipilimumab and nivolumab can be administered safely over 30 min with an acceptably low risk of IRRs (≤ 2.2%; ≤ 1/46). The excellent tolerability of the shortened infusions led to continuation of the fast infusion protocol at our institution, thereby increasing patient's convenience and allowing better health care resource utilization.

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Compliance with ethical standards

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Conflict of interest Maximilian Gassenmaier received travel support from Novartis, Merck Sharp & Dohme (MSD) and Bristol-Myers Squibb (BMS). Hans-Peter Lipp reports honoraria as a speaker from BMS, MSD and AstraZeneca. Thomas Kurt Eigentler reports honoraria as a speaker from BMS, MSD, Roche and Novartis. He is advisory board member of Roche and BMS. Dennis Doecker received travel support from BMS. Nikolaus Benjamin Wagner received travel support from Novartis. Andrea Forschner reports honoraria as a speaker from BMS, MSD, Roche and Novartis. She is advisory board member of Roche and Novartis and received travel support from Roche, Novartis and BMS. Claus Garbe reports grants and personal fees from BMS during the conduct of the study; grants and personal fees from Roche, Novartis and personal fees from Amgen, MSD and Philogen outside the submitted work. Alexander Scheu, Alisa Mueller and Lukas Kofler declare that they have no conflict of interest.

Ethical approval This study was approved by the ethics board of the University Hospital Tuebingen (project number 202/2017B02).

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

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