Efficacy and safety of ipilimumab in patients with pre-treated, uveal melanoma


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Background: Patients with advanced uveal melanoma have a poor prognosis and limited treatment options. Ipilimumab is approved for pre-treated adult patients with advanced melanoma. However, because previous clinical trials with ipilimumab have excluded patients with uveal melanoma, data in this patient population are limited.

Patients and methods: Pre-treated patients with advanced uveal melanoma received ipilimumab 3 mg/kg through an expanded access programme, every 3 weeks for four doses. Tumour assessments were conducted at baseline and after completion of treatment and patients were monitored throughout for adverse events.

Results: Among 82 assessable patients, 4 (5%) had an immune-related objective response and 24 (29%) had immune-related stable disease lasting ≥3 months for an immune-related disease control rate of 34%. With a median follow-up of 5.6 months, median overall survival (OS) was 6.0 months and median progression-free survival (PFS) was 3.6 months. The 1-year rates of OS and PFS were 31% and 11%, respectively. The safety profile of ipilimumab was similar to that in patients with cutaneous melanoma.

Conclusions: These data suggest ipilimumab 3 mg/kg is a feasible option in pre-treated patients with metastatic uveal melanoma. Evidence of disease control and a 1-year survival rate of 31% indicate the need for further investigation in randomised, controlled trials to determine the optimal timing and use of ipilimumab in this patient population.

Key words: efficacy, expanded access programme, ipilimumab, metastatic melanoma, uveal melanoma, safety

Introduction

Uveal melanoma is a highly malignant neoplasm that involves the vascular layers of the eye (iris, ciliary body and choroid), collectively known as the uvea. The estimated global incidence of uveal melanoma is between 5.3 and 10.9 cases per million inhabitants per year, and this estimate has changed little over the last 30 years [1]. Despite comprising only 3% of melanoma cases, uveal melanoma is the most common form of intra-uveal malignancy (85%) [2].

Uveal melanomas predominantly metastasise to the liver (around 90% of metastatic cases) although dissemination to the lung, bone and skin are also reported [3]. The strong tendency of uveal melanomas to spread regardless of early treatment has led to speculation that some patients already carry micrometastases at the time of diagnosis [2, 4, 5]. Once metastases have developed, patients with uveal melanoma have a poor prognosis. The Collaborative Ocular Melanoma Study (COMS) identified a 10-year overall metastasis rate of 34%, with 80% of these patients dying within 1 year of diagnosis of metastatic disease [3]. The median survival in patients with liver metastases is around 6 months [3], while patients with metastases confined to extra-hepatic sites have a slightly longer estimated survival of 19–28 months [4].

Brachytherapy and radiotherapy are available for the treatment of small local tumours, and enucleation for large primary uveal melanomas [6, 7]; however, patients with metastatic uveal melanoma have limited treatment options. Similar to cutaneous melanoma, available systemic therapies include dacarbazine (DTIC), fotemustine and cisplatin, as well as combination therapies such as the BOLD regimen (bleomycin, vincristine, lomustine and DTIC), with or without...
the addition of interferon [8]. However, no systemic treatment has been shown to improve survival of patients with metastatic disease beyond that predicted by the natural history of uveal melanoma [1, 9]. Further, unlike cutaneous melanomas, several studies report a lack of BRAF mutations in uveal melanomas, suggesting targeted therapy with BRAF kinase inhibitors may not be appropriate for patients with advanced uveal melanoma [10–13]. Although oncogenic mutations in G-protein α-subunits (GNAQ) and 11 (GNA11) have been described in uveal melanomas [14], no therapeutic agents have yet been developed which target these genes. Due to the poor prognosis of patients with hepatic metastases, various loco-regional therapies have been developed, targeting the liver directly with radiotherapy, immunotherapy or chemotherapy drugs. Although liver directed therapies such as radioisopheres or transarterial chemoembolisation are somewhat effective in controlling hepatic lesions, further disease progression in extra-hepatic sites remains a challenge with these treatments [15].

Patients with advanced cutaneous melanoma have a new treatment option in the form of ipilimumab, a monoclonal antibody against cytotoxic T-lymphocyte-associated antigen-4. Ipilimumab was the first anti-cancer agent to significantly improve overall survival (OS) in patients with previously treated advanced (unresectable or metastatic) melanoma in a randomised phase III trial [16] and was subsequently approved in this indication in the European Union. Ipilimumab also received US Food and Drug Administration approval for the treatment of previously untreated and pretreated adult patients with advanced melanoma. In the registrational phase III trial MDX010-20, ipilimumab demonstrated a near doubling of 1-year and 2-year survival rates and extended median OS compared with the comparator gp100. Most adverse events (AEs) observed with ipilimumab are related to its immune mechanism of action and most frequently affect the skin and gastrointestinal tract [16]. Immune-related AEs (irAEs) are generally manageable according to product-specific guidelines, which recommend appropriate medical therapy and/or treatment interruption or discontinuation [17].

Patients with primary uveal melanoma are frequently excluded from clinical trials because they are thought to have poorer response rates and survival outcomes than patients with advanced, cutaneous melanoma. As a result, patients with metastatic uveal melanoma are under-represented in prospective studies and data regarding the use of novel treatments are limited. An expanded access programme (EAP) of ipilimumab 3 mg/kg provided the opportunity to treat patients affected by metastatic uveal melanoma in a setting that closely reflected daily clinical practice. Here, we report the findings of the efficacy and safety of ipilimumab in patients with uveal melanoma treated at Italian Medical Centres participating in the European EAP.

patients and methods

study design and data collection

Patients with stage IV uveal melanoma were eligible to be included in the EAP if they had failed prior systemic therapy or were intolerant to at least one systemic treatment and if no alternative treatment option was available. An Eastern Co-operative Oncology Group (ECOG) performance status of 0, 1 or 2 was required, and an interval of at least 28 days since treatment with chemotherapy, biochemotherapy, surgery, radiation or immunotherapy was recommended. The EAP protocol was approved by the local independent ethics committees and all participating patients provided signed informed consent before enrolment.

Ipilimumab 3 mg/kg was administered intravenously over 90 min once every 3 weeks for a maximum of 4 doses. Tumour assessments were conducted at baseline and after completion of treatment (Week 12), and classified according to immune-related response criteria (irRC) [18]. Clinical response was defined as a complete response (irCR; disappearance of all index lesions), partial response (irPR; ≥50% decrease in tumour burden compared with baseline), progressive disease (irPD; ≥25% increase in tumour burden compared with nadir) or stable disease (irSD; criteria not met for CR, PR or PD). Immune-related disease control (irDC) was defined as irSD lasting ≥3 months, or an irPR, or irCR, and the disease control rate (irDCR) was the percentage of patients achieving irDC. Patients who progressed after initial irDC were eligible for retreatment with the same dosing and schedule. AEAs, including irAEs were monitored continuously and graded according to the Common Terminology Criteria for Adverse Events, version 3.0. In the absence of dose-limiting toxic effects, all four doses of ipilimumab were administered over the initial 12 weeks even if the patient appeared to undergo clinical progression, providing the patient’s performance status remained stable.

objectives

The aim of this analysis was to evaluate the efficacy and safety of ipilimumab 3 mg/kg in patients with metastatic uveal melanoma, to assess its feasibility as a treatment option in this patient population.

statistical analysis

Patient and disease characteristics were analysed using descriptive statistics, and expressed as relative frequencies (percentages) for discrete variables and median for continuous variables. Progression-free survival (PFS) and OS were estimated using Kaplan–Meier analysis and expressed as median values with corresponding two-sided 95% confidence intervals (CIs). Differences between survival curves were evaluated using the log-rank test.

results

patient characteristics and treatment

Of the 855 patients eligible for analysis within the EAP, 83 patients (10%) had uveal melanoma. Among these 83 patients, 60 (72%) received all four doses, 12 (15%) received three doses, 8 (10%) received two doses and 3 (4%) received one dose of ipilimumab 3 mg/kg. Reasons for not completing all four doses of ipilimumab therapy comprised disease progression (n = 11), death (n = 1), dose skipping (n = 2), AE unrelated to ipilimumab (n = 1) and tumour lysis syndrome (n = 1). Seven patients (8%) were retreated with ipilimumab following progression; two had an initial irPR and five had irSD lasting ≥3 months. Among the 83 patients, 72 (87%) had metastases to the liver and 1 had brain metastases. Sites of metastases for the remaining 10 patients were not specified. Baseline patient and disease characteristics are provided in Table 1.
Among 82 patients with uveal melanoma who were assessable for tumour response (1 patient was lost to follow-up), 4 had an irPR for an immune-related best overall response rate (irBORR) of 5%. An additional 24 patients had irSD; therefore, the irDCR was 34%. With a median follow-up of 5.6 months (range 1–28 months, interquartile range 3–11 months), the median OS was 6.0 months (95% CI 4.3–7.7; Figure 1A) and median PFS was 3.6 months (95% CI 2.8–4.4; Figure 1B). The estimated 1-year OS and PFS rates were 31% and 11%, respectively. Elevated LDH at baseline (>480 U/l) was associated with a worse prognosis (median OS, 3.0 months versus 11.6 months; \(P < 0.0001\)).

Of the seven patients retreated with ipilimumab upon disease progression, three regained disease control (one patient with an irPR and two with irSD).

efficacy

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safety

Of the 83 patients treated with ipilimumab, 47 (57%) reported an AE of any grade. These were considered to be treatment-related in 35 patients (42%; Table 2). Eight patients (10%) experienced grade 3 or 4 AEs, and these were considered to be ipilimumab-related in five patients (6%). The most common treatment-related AEs of any grade affected the skin (pruritus and rash), and the most frequent grade 3 or 4 AEs considered related to ipilimumab were liver toxic effect and diarrhoea. AEs were generally reversible when managed as per protocol-specific guidelines and median time to resolution of treatment-related AEs was 2.1 weeks (range 0.1–5.0 weeks).

discussion

The recent approval of the novel immunotherapeutic agent ipilimumab has changed the treatment of advanced cutaneous melanoma and provides optimism for patients with this disease. However, clinical trials with ipilimumab have so far excluded patients with primary uveal melanoma, so data on its efficacy and safety in this patient population are limited. Efficacy and safety data have previously been reported for a small number of patients with advanced uveal melanoma treated with...
compassionate use ipilimumab at a dose of 3 mg/kg [19] or 10 mg/kg [20]. No objective responses were observed in either of these analyses although two of the five patients treated with ipilimumab 3 mg/kg had durable SD [19]; of the 13 patients who received ipilimumab 10 mg/kg, 2 had SD and a third patient achieved SD after initial disease progression [20]. Among a further 20 patients treated with ipilimumab at the Memorial Sloan-Kettering Cancer Centre, 1 had a PR and 7 had SD at 12 weeks [21].

Our findings, from a much larger patient cohort, provide further evidence that ipilimumab at a dose of 3 mg/kg is clinically active in some patients with advanced uveal melanoma that is refractory to other treatments, lending further support to the therapeutic potential of ipilimumab in a disease setting where treatment options are lacking. Disease control was achieved in 34% of 82 patients (4 with irPR and 24 with irSD) and the 1-year OS rate was 31%. These results are consistent with data from patients with metastatic uveal melanoma who received ipilimumab 3 or 10 mg/kg in previous studies [19–21]. Although objective responses with ipilimumab were infrequent, DCRs are in line with those observed following ipilimumab treatment in patients with advanced cutaneous melanoma, where ipilimumab has demonstrated long-term survival benefits [22, 23].

Standard chemotherapy provides little improvement over palliative care in the prognosis of patients with advanced uveal melanoma despite objective response rates of up to 36% [24, 25]. Because of the time it takes to mount an anti-tumour immune response, the nature of response to immunotherapy differs from that with traditional chemotherapy. Responses to ipilimumab may take longer to evolve and intra-lesional inflammation or T-cell infiltration can appear as apparent disease progression. Although responses with immunological treatments may demonstrate a slower onset, they are often durable [18, 23]. Furthermore, in the absence of confirmed progression, patients with new lesions or growth of existing lesions may still experience long-term survival benefits with ipilimumab and should receive all four doses of ipilimumab as tolerated, providing their performance status remains stable [18, 20, 26].

The findings described here are consistent with reports of irSD being the most common outcome with ipilimumab in clinical trials. IrSD has been shown to be durable in many patients and can evolve into an irPR or even an irCR over time. Even in the absence of an objective response, irSD may last for months or years, and is associated with prolonged patient survival [27].

The safety profile of ipilimumab in our study was similar to that observed in patients with cutaneous melanoma in phase II and III clinical trials [17], with the majority of AEs being immune-related and consistent with ipilimumab’s proposed mechanism of action. It is notable that one of the most frequent treatment-related grade 3 or 4 AEs was liver toxic effect given the high frequency of hepatic metastases in patients with uveal melanoma. It is possible that, although attributed to ipilimumab, symptoms may have reflected disease progression within the liver rather than an AE per se; however, this requires further clinical investigation. One patient had tumour lysis syndrome. This rare complication affects <1 in every 100 patients treated with ipilimumab, and can generally be managed with agents used primarily to treat hyperuricaemia [28]. Most of the treatment-related AEs were mild, and AEs were generally reversible using protocol-specific treatment guidelines established previously in clinical trials [17]. The successful management of AEs in patients with uveal melanoma within the EAP setting suggests ipilimumab is a feasible treatment option in clinical practice.

conclusions
Overall, the data presented for patients treated with ipilimumab at centres in Italy, together with previous analyses of smaller patient groups, suggest that patients with advanced uveal melanoma may benefit from ipilimumab treatment. Ipilimumab showed clinical activity in pre-treated patients with uveal melanoma and was found to have a manageable toxic effect profile in this patient population. In subjects with metastatic cutaneous melanoma, ipilimumab has been shown to induce durable clinical responses and long-term survival benefits in clinical trials. Continued follow-up of our study population will provide long-term efficacy and safety data from patients with advanced uveal melanoma. Further investigation in randomised, controlled clinical trials is also warranted to determine the optimal application for ipilimumab.

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disclosure
MM has had an advisory role for and has received honoraria from Bristol-Myers Squibb. RD has received honoraria from Bristol-Myers Squibb for meeting presentations. VCS has had an advisory role Bristol-Myers Squibb, GlaxoSmithKline, Merck Sharp and Dohme and Roche. PQ has worked in an advisory role for Bristol-Myers Squibb, Roche and GlaxoSmithKline. PM is a member of the speakers bureau for Bristol-Myers Squibb, GlaxoSmithKline and Novartis. PAA has served as a consultant or in an advisory role for Bristol-Myers Squibb, Merck Sharp and Dohme, Roche-Genentech, GlaxoSmithKline, Amgen, Celgene, Medimmune and Novartis; he has received honoraria from Bristol-Myers Squibb, Merck Sharp and Dohme and Roche-Genentech. None of the other authors have any conflicts of interest to declare.
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