Case Report

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COMPLETE RESPONSE OF CUTANEOUS METASTASIS IN A MELANOMA PATIENT TREATED WITH IPILIMUMAB.

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SUMMARY

We present the case of a 58 year old woman, who achieved complete response for her cutaneous melanoma metastasis after treatment with ipilimumab at 3 mg/Kg. The patient was given dacarbazine as a first line treatment for her cutaneous metastasis and a partial response was achieved. However, after 26 cycles of chemotherapy, the cutaneous lesions progressed, so ipilimumab was chosen as a second line treatment. The patient was eligible for the compassionate use of ipilimumab.Two weeks after the fourth cycle with ipilimumab, a complete response of most cutaneous metastasis was noted, with a partial response of the remaining lesions, which were still regressing at the last follow-up visit. Ipilimumab, which was recently reported to improve survival in patients with metastatic melanoma, represents a most promising immunotherapeutic drug and it has been approved for patients with advanced melanoma as a first- and second-line treatment by the FDA and as a second-line treatment by the European Medicines Agency (EMA).

Introduction

We present the case of a 58 year old, woman, who achieved complete response for her cutaneous melanoma metastasis after treatment with ipilimumab at 3 mg/Kg. In March 2008 the patient underwent a lesion excision from the skin of her right leg, which was diagnosed as a 1.71 mm thick non ulcerated malignant melanoma,,presenting 1-6 mitosis per HPF (pT2a according to the 2009 AJCC melanoma staging and classification). In addition to the wide excision, three sentinel lymph nodes were excised. Since one of them was positive for micrometastasis, an inguinocruroiliac dissection was performed: of 16 lymph nodes, none carried melanoma metastasis (pN1a). A CT-scan was negative for distant metastasis (M0).

In October 2008, the patient showed several lesions on the right leg, clinically consistent with melanoma metastasis: a biopsy confirmed their histology. The patient was not eligible for hyperthermic antiblastic perfusion with tumor necrosis factor alpha and Melphalan, so she started therapy with low-dose interferon-alpha. Since no response was achieved with interferon alpha, in February 2009 the patient started chemotherapy with dacarbazin 800 mg/m^2 every 3 weeks. A partial response of the cutaneous metastasis was noted after 4 cycles, so treatment with dacarbazin was continued. In the meanwhile, the patient was monitored with PET/CTs, CT-scans and abdomen-US, confirming the absence of other metastasis. After 26 cycles of dacarbazin, the cutaneous lesions progressed, so a second line treatment with ipilimumab was chosen. The patient was eligi-

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ble for the compassionate use of ipilimumab at 3 mg/Kg every 3 weeks for 4 cycles. No drug-related toxicity was noted.
Figure 1 shows the cutaneous metastasis before treatment with ipilimumab.

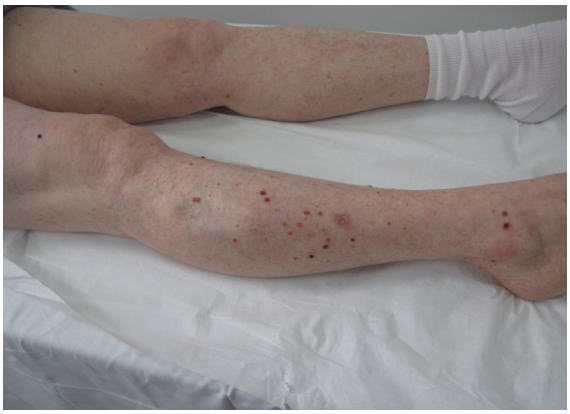

Figure 1: Cutaneous metastasis two days before treatment with Ipilimumab.

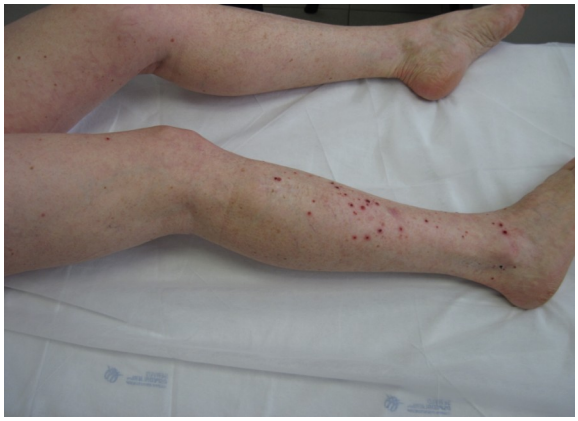

Figure 2: Apparent progression of the cutaneous metastasis after two cycles of Ipilimumab.

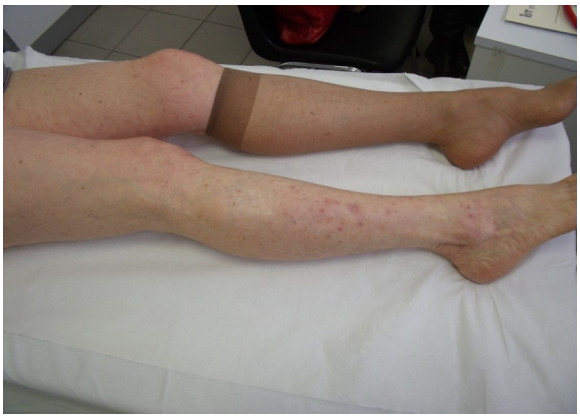

Figure 3: Complete response of most cutaneous metastasis and a partial response of the remaining lesions two weeks after the last cycle with Ipilimumab.

After two cycles (week 7), an apparent progression of the lesions was noted, consisting of an increase in their diameters and bleeding from some of them (Figure 2). Two weeks after the fourth cycle with ipilimumab (week 12), a complete response of most cutaneous metastasis was noted, with a partial response of the remaining lesions (Figure 3), which were still regressing at last follow-up visit (week 16).

Discussion

The incidence of cutaneous melanoma is increasing faster than any other cancer in the United States. Overall, melanoma incidence has increased 3.1% annually over the last 20 years. In 2007 the incidence rate in the United States was 27.5/100.000 in whites and 1.1/100.000 in blacks (1). Prognosis for advanced and metastatic melanoma is poor, with a 5-year survival of 78%, 59% and 40% for patients with stage IIIA, IIIB and IIIC respectively, and a 1-year survival of 62% for M1a, 53% for M1b and 33% for M1c (2).
The unsatisfactory results of the current standard therapies for metastatic melanoma highlight the need for effective new therapeutic strategies. Several drugs are currently under investigation as part of large clinical trials.
In recent years immunologic science has evolved and new mechanisms for targeted immunotherapies have been discovered. Immunotherapeutic agents are characterized by different clinical features compared to chemotherapy drugs. In clinical terms, it means that the traditional chemotherapy paradigms cannot be applied to immunotherapy, which presents different response patterns to treatment. Therefore, new immune-related response criteria (irRC) need to be adapted from standard RECIST and WHO criteria, designed to capture effects of cytotoxic agent, in order to correctly assess the response to immunotherapeutic agents. The spectrum of clinical patterns of antitumor response for immunotherapeutic drugs extends beyond that of cytotoxic agents and includes two conventional patterns (immediate response in baseline lesions and durable stable disease, possibly with a slow but steady decline in total tumor burden) and two novel patterns (response after tumor burden increase and response of index lesions in the presence of new lesions). The novel patterns are specifically recognized with

immunotherapeutic agents and probably depend on tumor infiltrating lymphocytes (3). The most promising immunotherapeutic drug is ipilimumab, which was recently reported to improve survival in patients with metastatic melanoma(4). Ipilimumab is a fully human monoclonal antibody (IgG1) that blocks cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), an immune checkpoint molecule that downregulates pathways of T-cell activation, to promote antitumor immunity (5). Hodi et al published data of a Phase III study which showed an improved survival in metastatic melanoma patients treated with ipilimumab in the NEJM of August 2010 (4). It was a randomized, double-blind study that enrolled 676 patients, including 82 patients who had, at baseline, metastasis in the CNS. Patients had all received previous treatment for metastatic melanoma. Patients were randomly assigned in a 3:1:1 ratio to treatment with solely ipilimumab, ipilimumab plus a gp100 peptide vaccine or gp100 plus placebo. Ipilimumab was administered at a dose of 3 mg per kilogram of body weight once every 21 days for four treatments. The median overall survival in the ipilimumab alone and ipilimumab plus gp100 groups was 10.0 and 10.1 months respectively, compared with 6.4 months in the gp100-alone group. That difference was statistically significant. The most common adverse events related to the study drug, which occurred in 60% of the patients treated with ipilimumab, were Immune-related events. The frequency of grade 3 or 4 immune-related adverse events (irAEs) was 10 to 15% in the ipilimumab groups. The irAEs mostly affected the skin and the gastrointestinal tract, the most common event being diarrhea, which occurred at any grade in 27 to 31% of the patients in the ipilimumab groups. Other common toxicities observed with ipilimumab included grade 3 and 4 irAEs such as dermatisis, hepatitis, uveitis and hypophysitis. The incidence of irAEs has been correlated with clinical response(6).

Most irAEs are manageable and generally reversible with corticosteroids. Long-term residual irAEs requiring treatment have been reported at 2-year follow-up and included primarily dermatological effects (rash, pruritus and vitiligo), colitis, and endocrine-related adverse events (7). Ipilimumab was also studied in combination with dacarbazine in a large Phase III trial: 502 patients with previously untreated metastatic melanoma were randomly assigned, at a 1:1 ratio, to ipilimumab (10 mg per kilogram) plus dacarbazine (850 mg per square meter of body-surface area) or dacarbazine (850 mg per square meter) plus placebo. The primary end point was overall survival, which was significantly longer in the group receiving ipilimumab plus dacarbazine than in the group receiving dacarbazine plus placebo (11.2 months vs. 9.1 months).

Higher survival rates were also seen in the ipilimumab-dacarbazine group at 1 year (47.3% vs. 36.3%), 2 years (28.5% vs. 17.9%), and 3 years (20.8% vs. 12.2%). Grade 3 or 4 adverse events occurred in 56.3% of patients treated with ipilimumab plus dacarbazine, as compared with 27.5% treated with dacarbazine and placebo (8).

From July 2010 to April 2011 ,the Italian Network for Tumour Biotherapy (NIBIT) conducted a Phase II study combining ipilimumab and fotemustine in patients with metastatic melanoma - the NIBIT-M1 Trial – with or without brain metastasis. 86 patients were enrolled (19 patients had evidence of brain metastasis and 2 patients had a history of them). Data were presented at the 2011 European Multidisciplinary Cancer Congress (Abstract No: 9305). As of April 2011, 28 patients had terminated the induction phase and 13 of them had already entered the maintenance phase; 43 patients were completing the induction phase and 15 had been withdrawn for AE severity or disease progression. Of the 17 patients for which tumor assessment at week 12 is available, 14 achieved disease control (CR, PR or SD), including brain metastases in 5 out of 6 patients, while 3 had PD.

Conclusions

In recent years immunotherapy has shown that it might be effective for the treatment of malignant tumors. Due to its biological characteristics and the fact that no effective treatment is currently available, melanoma represents a suitable target for immunologic research. Ipilimumab has been approved for patients with advanced melanoma in first- and second-line treatment by the FDA and in second-line treatment by the European Medicines Agency (EMA). Its efficacy has finally been demonstrated, but regrettably not all patients respond to the

drug in the same way as the patient we have presented. Researchers should now address their efforts to the understanding of predictive variables of response to treatment.

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