Case Report

Euromediterranean Biomedical Journal
for young doctors
(formerly: Capsula Eburnea)

Unconventional pattern of response in a metastatic melanoma patient treated with ipilimumab.

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SUMMARY

We present the case of a 74 year old man who achieved a complete response for hepatic and cutaneous metastasis and stabilization of his lymph node metastases after treatment with ipilimumab at 10 mg/Kg.
The patient was diagnosed with right foot cutaneous melanoma in February 2004.
In October the patient became metastatic and he underwent three different lines of traditional chemotherapy (Fotemustine, Dacarbazin and Carboplatin with Thalidomide) but each time a progression of the disease was noted. Consequently, the patient was enrolled in Protocol CA180008 and treated with ipilimumab 10mg/Kg every 3 weeks for 4 cycles.
Ipilimumab has been established as a drug able to induce long-lasting responses, and has been approved for patients with metastatic melanoma in first- and second-line treatment by the FDA and in second-line treatment by the EMA.

Case presentation.

We present the case of a 74 year old man who achieved a complete response and stabilization of his hepatic and lymph node metastases respectively after treatment with ipilimumab at 10 mg/Kg.
The patient was diagnosed with right foot cutaneous melanoma in February 2004 (pT4apN2a according to the 2009 AJCC melanoma staging and classification). In October 2004, he started a first line chemotherapy treatment with fotemustine 100mg/Kg q21 as some inguinal, iliac and interaortocaval lymph node metastases had appeared. After 8 cycles of fotemustine, he experienced a relapse of his lymph node metastases, so a second line treatment with dacarbazin 1000 mg/m^2 q21 was administered until a new progression was noted (after 6 cycles). A third line treatment with weekly carboplatin and thalidomide kept the patient stable for almost 8 months, but then a further new progression was noted with the appearance of multiple cutaneous metastases on his right leg and a 25-mm hepatic metastasis (Figure 1). Therefore, the patient was enrolled in Protocol CA180008 and treated with ipilimumab 10mg/Kg every 3 weeks for 4 cycles. The only drug-related toxicity was grade 1 diarrhea and vitiligo. The first tumor assessment was performed with a CT-scan two weeks after the fourth ipilimumab administration (week 12), and then every 4-6 months. Initially, a partial response of the index hepatic

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***Received**: March 20th, 2012 — **Revised**: April 22nd, 2012 — **Accepted**: May 4th, 2012*

metastasis was achieved; however, other smaller hepatic metastases appeared (Figure 2). The cutaneous and lymph node metastases were stable. At week 22, contemporary to the appearance of vitiligo on patient's face, limbs, trunk and hands, an initial regression of the cutaneous metastases was noted. At week 64, a regression of the hepatic (Figure 3) and cutaneous metastases was documented and those of the lymph nodes were stable. The cutaneous and hepatic metastases continued to reduce until the achievement of a complete response of most lesions and the stabilization of the remaining ones. At the last follow-up visit, more than four years after the first ipilimumab administration, the lymph node metastases were stable and the cutaneous and hepatic metastases were still responding. The patient was asymptomatic and in good clinical condition.

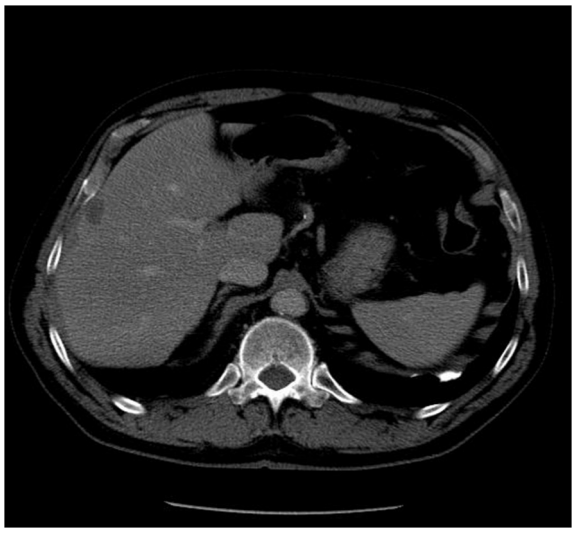

Figure 1: hepatic metastasis at baseline

Discussion

In the United States, the incidence of melanoma has increased from 6 cases per 100,000 inhabitants in 1970 to 18 cases per 100,000 inhabitants in 2000. In the same period, in the countries of Central Europe, the incidence rates have increased from 3-4 to 10-15 cases per 100,000 cases; therefore, showing a trend similar the United States(1). In Italy in 2011 it is estimated that there were almost 13,000 new diagnoses of melanoma. Although melanoma represents only 2-3% of all cancers, compared to others it has a high frequency in subjects under 50 years-old (5 -10% of the total in both sexes) (2).

The survival rate for patients with metastatic melanoma is low. Between 10 and 20% of patients survive up to two years after diagnosis. Although dacarbazine has never been shown to improve survival in randomized clinical trials, it is the drug of choice because it has a response rate of between 5 and 20%(3).

New treatment strategies include immunomodulatory antibodies that antagonize the receptor suppressing the immune response (such as anti-CTLA4 and anti-PD1

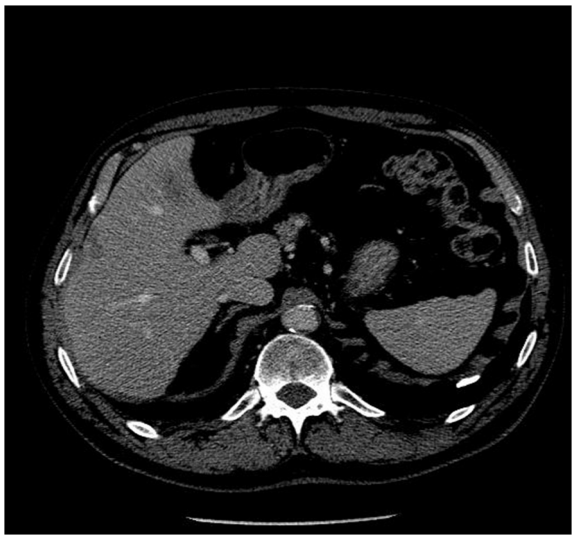

Figure 2: two weeks after the fourth ipilimumab administration (week 12), a partial response of the index hepatic metastasis

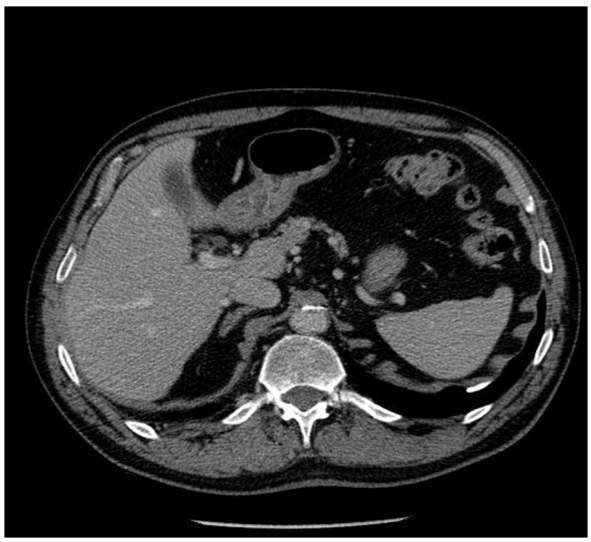

Figure 3: regression of the hepatic metastasis at week 64

or antibodies activating receptors that amplify the immune response such as anti-OX40 or anti-CD40). All are currently in Phase I and II except for Ipilimumab. This was the first drug shown to increase survival in cases of metastatic melanoma. Ipilimumab is an IgG1 antibody that blocks the CTLA4, which exerts negative regulatory activity, thereby increasing the activation and proliferation of T cells(4).

In the NEJM of August 2010, Hodi et al published the results of a Phase III study which finally demonstrated an improved survival for metastatic melanoma patients treated with ipilimumab(5).

Ipilimumab is associated with adverse inflammatory reactions resulting from increased or excessive immune activity (immune-related adverse events, irAEs), reflecting its mechanism of action.

The most common adverse events related to the study drugs were immune-related events (irAEs), which occurred in 60% of the patients treated with ipilimumab. The immune-related adverse events mainly involved the skin and the gastrointestinal tract, the most common event being diarrhea (27 to 31% of the patients). Other common toxicities observed with ipilimumab were dermatisis, hepatitis, uveitis and hypophysitis. The incidence of irAEs has been correlated with clinical response (6). Immune-related AEs were generally managed with either symptomatic therapy for Grade 1-2 events, systemic corticosteroids for Grade 3-4 events, or other immunosuppressants for steroid-unresponsive GI or hepatic irAEs, as appropriate.

Management of irAEs was usually paired with omission of dosing for mild or moderate events and permanent discontinuation for severe irAEs.

Long-term residual irAEs included primarily dermatologic effects (rash, vitiligo and pruritus), colitis, and endocrine-related adverse events(7).

Conclusions.

Treatment for patients with metastatic melanoma has changed rapidly over the last few years and immunotherapy has been shown to possibly be effective in the management of malignant tumors.

Ipilimumab has been established as a drug capable of inducing long-lasting responses and has been approved for patients with metastatic melanoma in first- and second-line treatment by the FDA and in second-line treatment by the EMA.

The drug's efficacy has finally been demonstrated, but regrettably not all patients respond to it in the same way as the patient we presented. For this reason, ipilimumab is being trailed clinically as part of combination treatments with other drugs, such as fotemustine, dacarbazine and bevacizumab; it will soon also be investigated in combination with target therapy (BRAF inhibitors).

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