Wspolczesna Onkol 2012; 16 (5): 363–370

DOI: 10.5114/wo.2012.31763

Review

What is new in the treatment of advanced melanoma? State of the art

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The incidence of melanoma is increasing steadily both in Poland and worldwide. Until 2010 three drugs were approved for the treatment of metastatic melanoma – dacarbazine (DTIC) in Europe and USA, fotemustine in Europe and interleukin-2 (IL-2) in USA. Approval of ipilimumab and vemurafenib in Europe and USA has changed the standard of care, while the next candidates such as dabrafenib and trametinib have improved survival in phase III studies in metastatic melanoma patients. An encouraging treatment strategy is the combination of dabrafenib and trametinib, evaluated in a phase I/II study with an ongoing phase III trial. Another promising new immune modulating monoclonal antibody (mAb) is anti-PD1 (BMS-936558), tested in an early phase trial in monotherapy or in combination with a multipeptide vaccine in metastatic melanoma patients. Ipilimumab or BRAF inhibitors (vemurafenib, dabrafenib) seem to be active in patients with brain metastases. Intensive research of melanoma vaccines is currently being carried out in a number of countries worldwide. However, no vaccine in the treatment of melanoma has been approved by regulatory authorities so far. Lack of effective therapy in patients with high-risk resected melanoma led to a number of clinical studies of adjuvant treatment. Interferon-α (INF-α) therapy in this setting is still controversial. A dendritic cell-based vaccine in a randomized phase II trial showed a survival benefit over the control group in patients with high-risk resected melanoma. Promising results of long-term survival of advanced resected melanoma patients in a phase II study evaluating the genetically modified tumour vaccine (GMTV) AGI-101 were reported.

This review provides an update on clinical strategies used or tested in patients with metastatic melanoma.

Key words: melanoma, BRAF inhibitor, immunotherapy, anti-CTLA4, cancer vaccines.

Introduction

The incidence of melanoma is increasing steadily both in Poland and worldwide. Melanoma presents the highest death rate among young people between 20 and 29 years of age. The mortality to incidence ratio in Poland is much higher than in Western Europe [1]. More than 2500 skin melanomas were diagnosed in Poland in 2009. Over 1000 patients will die each year due to metastatic disease [2]. Thus, there is a critical need to improve the understanding, prevention, and treatment of this malignancy.

Until 2010 three drugs were approved for the treatment of metastatic melanoma – dacarbazine (DTIC) in Europe and USA, fotemustine in Europe and interleukin-2 (IL-2) in USA. However, none of these drugs showed beneficial effects on survival of patients in phase III trials. Although objective responses after standard treatment are being observed, as well as a few long-term remissions after IL-2 (less frequently after chemotherapy), no predictive factors for these treatment strategies are known. Multidrug chemotherapy consisting of DTIC (BOLD, CVD, Dartmouth) results in a higher response rate, although is not beneficial in terms of survival over DTIC alone. Also commonly used temozolomide or paclitaxel with or without carboplatin did not result in overall survival (OS) prolongation [1]. In addition, various strategies of combining chemotherapy with biotherapy did not bring significant benefits to patients [3].

Recent approval of ipilimumab and vemurafenib in Europe and USA changed the standard of care of metastatic melanoma patients. Moreover, positive results of phase III trials evaluating dabrafenib and trametinib may lead to approval of these drugs in the near future. A number of new small molecules or immunotherapy strategies are currently in various stages of clinical development in metastatic melanoma.

Lack of effective treatment in patients with high-risk resected melanoma led to a number of clinical trials. Several randomised phase III studies evaluating interferon (IFN)-α-2a and IFN-α-2b in low, medium and high doses have been carried out. Only in two of them was a statistically significant improvement of OS observed. High-dose IFN-α-2b (Intron®) has been approved by the U.S. FDA (Food and Drug Administration) based on the results of the ECOG 1684 trial. At a median follow-up of 6.9 years the study demonstrated a statistically significant improvement in survival for patients treated with IFN-α-2b compared to the control group. However, at 12.6 years of follow-up, OS was not significantly different between the two study groups. Intron is indicated in patients after resection of high-risk melanoma (stage IIB and stage III). Recently (March 2011) pegylated-IFN-α-2b (Sylatron®) has been approved for the treatment of patients with melanoma with microscopic or gross nodal involvement after definitive surgical resection including complete lymphadenectomy. The approval was based on the results of the EORTC 18991 trial. The study demonstrated a lack of survival benefit with the improvement in recurrence-free survival (RFS) in unselected patients treated with Sylatron compared to the placebo control [4].