Advanced skin melanoma – systemic treatment

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ABSTRACT

In Poland, morbidity and mortality rates for melanoma are constantly increasing. In the case of inoperable disease or distant metastases, prognosis remains poor. For many years, dacarbazine has been the gold standard in systemic treatment. Recently, a significant progress in melanoma therapy has been observed. Introducing targeted therapy or immunotherapy significantly improved treatment outcomes. This review paper presents current knowledge on systemic treatment of advanced melanoma, including treatment availability in Poland.

KEY WORDS: melanoma, systemic therapy, immunotherapy

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INTRODUCTION

Skin melanoma accounts for nearly 2% of all malignant neoplasms in Poland. For many years, melanoma-related morbidity and mortality have been on the rise in both gender groups and in all age brackets. In 2010 in Poland, 1195 cases of melanoma were recorded (621 deaths) in males, and 1350 (570 deaths) in females [1]. Treatment results continue to deteriorate in our country when compared to other European Union states, with the 5-year survival index amounting to around 71% for female patients and around 56% for male patients in the years 2003–2005 [2]. The prognosis is poor for metastatic diseas, with the mean overall survival (OS) totalling around 6.2 months. Only 3–4% of patients survive 5 years [3].

For many years, the number of therapeutic options for metastatic melanoma was highly limited. In recent years, however, we have witnessed a rapid progress with reference to systemic treatment. Advances in molecular biology have offered insight into the mutation mechanisms of the genes involved in carcinogenesis. Apart from the conventional chemotherapy, targeted molecular drugs have been developed as well as immunotherapy, giving the patients a considerable chance to improve their disease prognosis.

The aim of the present paper is to review the existing therapeutic options related to the systemic treatment of stage 4 melanoma.

CHEMOTHERAPY

Dacarbazine (DTIC) was registered for palliative treatment of melanoma both by the American Food and Drug Administration (FDA) as well as by the European Medicines Agency (EMA) already in the 1970s.

It is a cytotoxic medication, synthesized towards the end of the 1950s, exhibiting alkylating properties, inhibiting incorporation of purines into DNA, and interfering with the sulfhydryl groups. The recommended dosing scheme is 200–250 mg/m² i.v. for 5 consecutive days, with chemotherapy courses repeated every 3 weeks. It is accepted (and frequently applied in medical practice) to administer the drug once every 3 weeks dosed at 850–1000 mg/m² i.v.

The average percentage of objective response is around 15%, and its duration does not exceed 6 months [3]. Generally speaking, the drug is well tolerated, with the chief adverse events being the loss of appetite, nausea, emesis and suppression of the bone marrow function. Despite the lack of prospective randomized controlled clinical studies comparing dacarbazine to placebo, it still remains the most important drug in melanoma "classical chemotherapy" and comparator for the majority of new study drugs under clinical evaluation. Moreover, it is often the only therapeutic option available, as other forms of treatment are disqualified.

Temozolomide, vinca alkaloids, platinum analogues, taxanes or nitrosourea derivatives have not been proven to extend the mean OS as compared to dacarbazine. Hence, they can be administered as subsequent lines of chemotherapy or as components of multi-drug schemes.

Additionally, multi-drug chemotherapy is significantly more toxic than DTIC, offering a higher percentage of response to treatment, but with no clear benefit as regards the overall survival [4].

MOLECULAR TARGETED THERAPIES

Numerous genetic mutations, significant for the pathogenesis of the disease, have been discovered in melanoma cells. Special therapeutic significance appears to be related to the hyperactivity of the RAS/RAF/MEK/ERK pathway, resulting most frequently from the point mutation of the BRAF kinase V600E gene. It is observed in around 40% of melanoma patients [5]. Prognosis of the BRAF mutation patients is not entirely clear. So far, only a single study has been published, confirming the prognosis of patients not treated with BRAF inhibitors to be statistically significantly poorer. The study carried out by Long et al. found that the mean OS for the BRAF mutation patients who are not treated with inhibitors amounts to 5.7 months. The mean OS for the wild BRAF patients was recorded as 8.5 months. On the other hand, no mean OS has been recorded for the BRAF mutation patients treated with inhibitors [6]. The authors' own experience goes to show that the BRAF mutation melanomas follow a dramatically rapid clinical course. The knowledge acquired thanks to fundamental research has contributed to the development of a new group of drugs, i.e. mutant kinase inhibitors. Representatives of this group are: vemurafenib, dabrafenib and trametinib.

Vemurafenib is a selective inhibitor of the mutant BRAF isoform. Phase III clinical trial (BRIM-3), comparing vemurafenib with dacarbazine in patients with the V600E BRAF mutation, has demonstrated considerable improvement in terms of objective response rate (ORR) and progression free survival (PFS), totalling respectively 48% vs. 5%, and 6.9 months vs. 1.6 months.

The mean OS was 13.2 and 9.6 months respectively [7]. Additionally, the drug is active in cases of CNS metastases. In the MO25653 study, the mean OS in that group of patients whose prognosis is especially poor, amounted to 5.3 months [8].

Vemurafenib is available as 240 mg tablets. Recommended dosage is 960 mg twice a day. In case of adverse events, the dose may be reduced to 480 mg twice daily. Major adverse events include hepatotoxicity, arthralgia, fatigue, dermal toxicity (rash, photophobia, pruritus), secondary skin neoplasms, e.g. squamous-cell carcinoma, nausea, and alopecia. Clinical practice has seen early response to treatment, frequently leading to a spectacular regression of even highly advanced lesions. However, development of secondary resistance to treatment is usually only a matter of time, with disease progression being quite rapid. The drug is available in Poland as part of the drug reimbursement programme.

Dabrafenib is another BRAF kinase inhibitor. Its efficacy has been evaluated in 3 randomized clinical trials: BRF113683 [BREAK-3], BRF113929 [BREAK-MB] and BRF113710 [BREAK-2]. The BREAK-3 study compared efficacy of dabrafenib with that of dacarbazine in patients with the V600E mutation of the BRAF gene. The mean PFS amounted to 5.1 and 2.7 months respectively [9]. The BREAK-MB study proved that dabrafenib is active in the treatment of BRAF melanoma CNS metastases. Finally, the BREAK-2 study is a phase II trial, looking into efficacy and safety profile of dabrafenib in the treatment of metastatic BRAF mutation melanoma. The recommended dosing scheme is 150 mg orally twice a day. The toxicity profile resembles that of vemurafenib, with fewer dermal complications though. Currently (September 2015), the drug is reimbursed in Poland [10].

Trametinib is a selective inhibitor of the MEK1 and MEK2 protein kinases. The METRIC phase III trial assessed its efficacy as compared to chemotherapy (dacarbazine or paclitaxel) in melanoma patients with confirmed BRAF V600E or V600K mutation. Mean PFS and ORR was 4.8 months vs. 1.5 months, and 22% vs. 8% respectively, while mean OS totalled 15.6 months and 11.3 months respectively [11]. The recommended daily dose of trametinib is 2 mg administered orally. The most common adverse events include rash, diarrhoea, fatigue, peripheral oedema, nausea and acne.

Combination of trametinib and BRAF inhibitors gives a chance for higher rate of response to treatment, and prolongation of the progression-free survival. Such a combined therapy makes it possible to arrive at the rate of 76% of objective remissions with PFS as long as 10 months [12]. Additionally, combination of different drugs reduces the BRAF inhibitor-related skin toxicity, but at the same time is more often observed to trigger complications such as fever or chills. The most recent results of the COMBI-v trial confirm superiority of combined therapy over BRAF inhibitor monotherapy [13]. This trial compared efficacy and safety of dabrafenib + trametinib therapy with wemurafenib monotherapy. Mean OS was 25,6 vs. 18,0 months respectively (HR 0.66 [95% CI, 0.53–0.81]) $p < 0.001$) and mean PFS amounted to 12,6 vs. 7,3 months respectively, in favour of dabrafenib with trametinib. At present (September 2015), trametinib is not available in Poland.

In summary, the available protein kinase inhibitors appear to be a very attractive option for palliative melanoma treatment. Their major advantage is the high response rate as well as the possibility to manage disease symptoms swiftly. The downside, on the other hand, is the fact that the group of patients who benefit from the above-mentioned treatment is limited to those with diagnosed mutation. Another disadvantage is the inevitable development of resistance to treatment.

IMMUNOTHERAPY

The origins of contemporary oncological immunotherapy go back to the end of the 1950s. Then, the concept of immunological surveillance was formulated by Burnet and Thomas, based on the premise that cancer cells are eliminated by the body's immune system. According to the theory, cancer develops when a part of the population of mutant cells ceases to be subject to immunological surveillance [14]. An indirect proof that the hypothesis is correct is the increased incidence of oncological diseases among people with compromised immune systems. Nowadays, the hypothesis has been modified to assume that there is a continuous interaction between the neoplasm and the immune system, and even if the body fails to defeat the tumour, its development and progression largely depend on the reactivity of the immune system [15].

So far, attempts at treating advanced melanoma with immunotherapy have not been successful and were related to serious complications or were too complex to be implemented as everyday medical practice. That situation has changed, once an entirely new class of drugs has been developed – anti-CTLA-4 and anti-PD-1/PD-L1 antibodies.

Ipilimumab is a breakthrough for several reasons. It is the first drug since dacarbazine which has led to prolonged survival of

advanced melanoma patients. Its mechanism of action heralds the era of immuno-oncology. In order to trigger the immune system response, it is necessary for the antigen to be presented by the APC cell (antigen-presenting cell) to the lymphocytes. Another signal is needed, though, to activate the T lymphocytes, i.e. stimulation of the CD28 molecule, found on their surface, by the B7 molecule located on the APC cell surface. Upon reception of the 2 signals, the lymphocytes are ready to destroy the cells on the surface of which certain antigens are found (e.g. antigens of neoplastic cells). Excessive activation of the immune system, however, might be highly dangerous and lead to autoaggression. Thus, the immune system comprises mechanisms inhibiting its excessive stimulation, with one of them being the CTLA-4 molecule found on the surface of the activated T cells. It exhibits a much higher affinity to the B7 molecule than the CD28 molecule. Once CTLA-4 binds with B7, the co-stimulation signal is interrupted, and the immune response is inhibited [16]. Ipilimumab is a human anti-CTLA-4 antibody. By binding with this molecule (on the surface of the T lymphocytes), it prevents the immune system response inhibition.

The registration trial compared ipilimumab with the gp100 vaccine. Mean OS was 10.1 vs. 6.4 months respectively [17]. The CA184-024 phase III trial, on the other hand, compared combined therapy involving ipilimumab and dacarbazine with efficacy of dacarbazine monotherapy. Mean OS was 11 vs. 9 months respectively [18]. The results obtained, even though statistically significant, do not appear to be a breakthrough at face value. However, there is a group of ipilimumab-treated patients (around 20%) who achieve long-term benefits from treatment [19]. Some even suggest that there may be cases of complete recovery from advanced melanoma. Ipilimumab's entirely new mechanism of action also requires a set of different criteria to assess response to treatment. The assessment should not be performed earlier than 12 weeks into therapy, and regression of lesions may occur after an initial period of pseudo-progression. That mechanism of action is also related to an entirely new spectrum of adverse events. Turning off the T lymphocyte inhibitory mechanism, ipilimumab may lead to autoimmunity symptoms, including immunological damage to the skin, alimentary tract, endocrine organs, liver, pancreas, kidneys and the nervous system. Severe adverse events (G3/G4) affect a dozen or so per cent of patients, leading to treatment cessation in around 10% of them [20, 21].

Ipilimumab is dosed at 3 mg/kg and is administered every 3 weeks as a 90-minute i.v. infusion. Complete treatment comprises 4 injections. The drug is available in Poland as part of the drug reimbursement programme financed by the National Health Fund. However, its use is restricted to the second line of treatment in our country. Taking into account its mechanism of action, and the late response to treatment, the therapy should be addressed to patients in good general condition, with no symptoms of autoaggression, and slow disease progression.

Other new immunological agents for the treatment of advanced melanoma include 2 anti-PD-1 antibodies: nivolumab and pembrolizumab. Their development is linked to another identified mechanism of inhibiting excessive activity of the immune system. The PD-1 (programmed death-1) receptors have been found on the surface of the activated T lymphocytes. The receptors may bind with the ligands (e.g. PDL-1, PDL-2) present on the cell surface (both healthy and neoplastic) to inhibit the immune response. Blocking the interaction of PD-1 with PDL-1 may prevent the development of immunological tolerance, thus enhancing the immune response towards certain tissues, including the cancer ones.

Nivolumab is a human anti-PD-1 antibody. Topolian et al. examined the effect of nivolumab in metastatic melanoma patients. Irrespectively of their BRAF status, the study included heavily and systemically pre-treated subjects (up to 5 lines of treatment) with CNS metastases (and on certain conditions). Mean OS reached nearly 17 months, and 2-year survival was over 40%. The most common adverse events included fatigue, rash and diarrhoea [22].

Pembrolizumab is yet another anti-PD-1 antibody. Ribas et al. recorded 34% of responses to treatment, with 1-year OS amounting to 70% (no mean OS achieved so far) in metastatic melanoma patients treated with pembrolizumab [23].

It would appear that anti-PD-1 antibodies have lower toxicity and generate earlier response to treatment than ipilimumab. Moreover, the response is a long-term one, and affects a greater percentage of patients.

In Poland, the two drugs – nivolumab and pembrolizumab – are available only in clinical trial settings.

SUMMARY

Despite a significant progress made in the recent years in the treatment of metastatic/inoperable melanoma, the disease is still associated with poor prognosis. The patients' situation deteriorates due to limited availability of the new classes of

drugs in Poland. Apart from the not very efficacious "classical" chemotherapy, vemurafenib, dabrafenib and ipilimumab (only as second-line treatment) are currently available as part of the national reimbursement programmes. The remaining drugs are only available in clinical trial settings. Therefore, all advanced melanoma patients should undergo treatment in referential centres with access to the reimbursement programmes and clinical trials. For patients who cannot qualify for a clinical trial, the therapeutic options are considerably limited. BRAF melanoma patients should be on vemurafenib or dabrafenib as first-line treatment, followed by ipilimumab in case of failure. Those with no BRAF mutation are left with dacarbazine as first-line treatment, and ipilimumab as the second-line one. It is worth emphasising that the registration provisions do not restrict the administration of ipilimumab to any of the systemic treatment lines. It is optimal that patients with slow disease progression be qualified for treatment, as response is usually observed only 3–4 months into therapy.

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Ida Cedrych – author of the concept and the paper's assumptions, proofreading and approval of the final version of the manuscript.