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Personalised medical management of patients with melanoma (part 2)

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In recent years, a dynamic increase has been observed in occurrence of melanomas, especially in young and middle-aged patients. This is the reason why curing these patients has become a priority also in the economic context. Melanomas belong to a group of neoplasms of very high genetic heterogeneity. The most common genetic alterations concern two signalling pathways: mitogen activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) pathway. Identification of the characteristic molecular changes in the neoplastic tissue allows optimisation and individualisation of the therapy. Thus, it contributes to an increase in successful cancer treatment, reduction of treatment side effects and to improvement of the patients' quality of life. Currently, the standard management of skin melanoma patients involves – along with surgical treatment and classical chemo/radiotherapy which is now less frequently used – also introduction of targeted therapy focused on molecular changes within the tumour tissue as well as immunotherapy which relies on activating the immune system.

Key words: melanoma, *BRAF*, *NRAS*, targeted therapy

The basic method of treating melanoma is surgery, which involves removal of the primary tumour with a relevant margin of unchanged tissue. The size of the margin depends on the depth of the melanoma infiltration. To detect micrometastases to the lymphatic system, sentinel lymph node biopsy (SLNB) is often additionally performed. Patients with pT1b-T4b stage of melanoma are routinely qualified for SLNB (after excluding disease dissemination). If cancer cells are found in a lymph node, radical lymphadenectomy remains an option for consideration [1]. Moreover, in order to reduce the risk of disease recurrence, in advanced cases (resectable stage III and IV tumours), adjuvant treatment aimed at molecular changes or immunotherapy is implemented. Patients with disseminated disease are treated with similar methods, but the treatment is palliative in their case.

Molecular changes-targeted treatment

BRAF

If V600 mutations are found in the *BRAF* gene in a metastatic melanoma, the treatment involves application of targeted BRAF inhibitors which are competitive to ATP (BRAFi) – vemurafenib (FDA recommendations from 2011) or dabrafenib (FDA recommendations from 2013) [2, 3]. BRAF inhibitors lead to tumour regression in approximately 90% of cases in metastatic

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patients with the *BRAF* V600 mutation. Response time varies from several months to more than 1.5 years [4].

Combined treatment – together with selective MEK inhibitors – is more effective than BRAFi monotherapy. Results from clinical trials on first-line treatment with trametinib (Mekinist) in combination with dabrafenib (Tafinlar) (COMBI-v and COMBI-d) showed a 5-year survival in approximately 30% of patients with metastatic or unresectable melanoma [5]. Also, clinical studies of patients treated with the combination therapy, i.e. cobimetinib (Cotellic) with vemurafenib (zelboraf) (coBRIM, BRIM-2, BRIM-3, BRIM-7) showed a higher median of overall survival (*OS*) and progression-free survival (PFS) compared to BRAFi monotherapy [6, 7]. However, both of these treatments have side effects such as fever and photosensitivity. On the other hand, with the combination of BRAF/MEK inhibitors (encorafenib + binimetinib), fewer side effects and high treatment efficacy are reported (COLUMBUS study) [4].

According to Polish recommendations, in line with ESMO and NCCN guidelines, in patients with confirmed *BRAF* mutation, combination therapy with BRAF and MEK inhibitors is recommended in certain clinical situations [1]. From September 2020, under the drug programme "Treatment of melanoma of the skin or mucous membranes" in patients with a BRAF activating V600 mutation and with metastatic or unresectable melanoma, state funding covers the molecularly targeted therapy: encorafenib (Braftovi) + binimetinib (Mektovi). Further, provisions regarding other combinations of BRAFi and MEKi have been standardised, which makes it easier for physicians to qualify patients for appropriate therapies.

Despite the use of combined treatment with two antibodies, resistance mechanism is often observed in patients, and some of them do not benefit from treatment at all. This means that further research is needed to help identify the mechanisms of resistance [8].

NRAS

Despite many years of research, targeted therapy in the form of direct inhibitors of the NRAS protein is still a serious challenge because small-molecule GTPase is a very difficult target for conventional drugs [9]. Therefore, research was focused on therapies targeted on (downstream) effector pathways activated by *NRAS*: MAPK and PI3K as the best-known ones in the aetiopathogenesis of melanomas. In patients with advanced melanoma and the *NRAS* mutation, promising results have been obtained so far for the MEK inhibitor (MEK-162) [10]. Such results have not yet been obtained for the PI3K pathway. Although clinical trials are still pending (e.g., NCT03932253), preliminary data suggest that molecularly targeted therapies (MEK1/2 inhibitors) will soon become available for this subset of patients.

KIT

So far, over a dozen clinical trials have been carried out concerning administration of various small molecule inhibitors of KIT. Imatinib (Glivec) – initially used against BCR-ABL fusion in chronic myeloid leukaemia - has also proven to be an effective KIT inhibitor. The best response was recorded in patients with exon 11 and 13 mutations and gene amplification.

Another KIT inhibitor is nilotinib (Tasigna), which is comparable or more potent than imatinib. Dasatinib also has anti-mutation / amplification activity against *KIT* and further targets Src family kinases. Sunitinib, which in addition to blocking *KIT*, inhibits also the vascular endothelial growth factor receptor (VEGFR), has also been approved for the treatment of melanoma [11]. Further, therapy targeted at *KIT* and downstream pathways may probably help control cancer progression. It was also shown that *KIT* inhibition contributed to enhancement of the immune response, thus increasing anti-neoplastic effect through activation of T lymphocytes and clonal expansion of cytotoxic cells (natural killers – NK). The results of studies on therapies applying KIT inhibitors indicate improvement in the general condition of patients and prolonged progression-free time. In single cases complete disease remission was observed. However, improvement occurs only in some of the treated patients, therefore, further studies are necessary in patients with mutations in the *KIT* gene [11].

Immunotherapy

One of the hallmarks of cancer is its ability to escape from the immune system's effects. However, the literature describes cases of patients with spontaneous activation of the immune system and cancer's auto-aggression [12]. This has brought scientists' attention to the potential for modulating the immune system to fight cancer.

In patients with unresectable or metastatic melanoma, the immune checkpoints is blocked, which in physiological conditions is responsible for maintaining homeostasis and preventing autoimmune reactions [12].

The first approved drug to block immune checkpoints was ipilimumab, a monoclonal antibody against a cytotoxic antigen (anti-CTLA-4 [cytotoxic T cell antigen 4]). CTLA-4 is an antigen present on the surface of activated T lymphocytes, which competes with CD28 for the binding of CD80 (B 7.1) and CD 86 (B 7.2) ligands present on the sufrace of antigen-presenting cells [13]. CD28 is constantly present on the surface of T cells and it is first to bind CD80 and CD86. This in turn triggers intracellular activation which leads to CTLA-4 translocation to the lymphocyte surface. In comparison to CD28, CTLA-4 has a greater affinity for CD80 and CD86 ligands. This leads to a silencing / inhibition of the immune reaction (negative feedback) [14]. Blocking CTLA-4 by ipilimumab does not suppress the immune response, and T cells remain active to fight cancer cells. However, the response to treatment with ipilimumab is observed only after several months, therefore the drug should be used in patients in good general condition. In addition, response is only seen in a small percentage of patients (approximately

10%) and immune-related adverse effects (irAEs) are serious. They include:

- inflammation of various tissues, most frequently the skin,
- gastrointestinal reactions (enteritis),
- hepatitis,
- endocrinopathies [15].

Much fewer side effects are observed in immunotherapy directed at the programmed death checkpoint, which is the PD-1 receptor (programmed cell death protein 1) present on T lymphocytes. Under physiological conditions, the PD-1 receptor binds with PD-L1 ligands (programmed death-ligand 1) and PD-L2 (programmed death-ligand 2) present on different cells of the body. Thus, autoimmune reactions are avoided [16, 17]. Frequently, overexpression of PD-L1 is observed on the surface of neoplastic cells, which is associated with "concealment" of the tumour from the immune system. Blocking the PD-1 receptor increases the activity of T lymphocytes [13].

Currently, two anti-PD-1 monoclonal antibodies are used in the immunotherapy of advanced melanoma: nivolumab and pembrolizumab. For both nivolumab and pembrolizumab, statistically significant increases in overall survival and progression-free survival were reported in patients with metastatic melanoma as compared to patients treated with ipilimumab [16, 17]. Interestingly, retrospective studies indicate that patients with the *NRAS* mutation gain more from immunotherapy than patients with other genetic changes [18, 19]. This is probably related to the increased expression of PD-L1 on the tumour cell surface in patients with the *NRAS* mutation.

Further clinical trials revealed that double blockade of the immune system's checkpoints by combined administration of ipilimumab and nivolumab increased the patients' progression-free survival and overall survival as compared to separate application of immunotherapies (Checkmate 067 and 069 studies). Additionally, trials concerning treatment with reduced dose of ipilimumab and prembrolizumab showed a strong antineoplastic effect, lasting response, positive long-term survival and controllable toxicity (KEYNOTE-029 study) [20–22].

In Poland, from 1 September 2020, a new therapeutic scheme (referred to as combo) is funded by the public health insurance system for a selected group of patients. It allows simultaneous administration of nivolumab (Opdivo) + ipilimumab (Yervoy) in a combination therapy as the first-line treatment of metastatic or unresectable melanoma. However, since January 2021, immunotherapy (pembrolizumab or nivolumab) and combined targeted therapy using BRAFi + MEKi (dabrafenib + trametinib) are available in the drug scheme as a part of adjuvant treatment in patients with stage III resectable melanoma. Thus, Polish patients have gained access to state-of-the-art treatment which reduces the recurrence risk by about 20%.

Conclusions

Genetic analysis of somatic changes in melanomas has allowed introduction of personalised therapy against oncogenes and/or signalling pathways that are activated as an expression of loss of function of genes that are essential in a given pathway. The best-known treatment target is inhibition of *BRAF* in patients with metastases and *BRAF* activating mutation. It has been shown that targeted therapy with BRAF inhibitors has a huge impact on the natural course of advanced melanoma, which in turn has led to development of new targeted therapies, including activation of natural defence mechanisms. Currently, drugs are sought that will inhibit both the primary and secondary pathways of oncogene activation, leading to the acquisition of resistance during treatment.

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