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Review article

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New developments in the perioperative treatment of melanomas with locoregional advancement

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Surgical intervention is the treatment of choice for patients with melanomas. However, the prognoses of the patients with melanomas at the IIC–IV stage, even after a complete resection of the lesions, is very diverse and, to a great degree, connected with a high risk of disease recurrence. The positive results of the studies in this area have resulted in systemic adjuvant therapy becoming the standard for patients in this group. New methods of systemic treatment – both the molecularly targeted treatment with BRAF and MEK inhibitors (dabrafenib with trametinib) and anti-PD-1 immunotherapy (nivolumab or pembrolizumab) – are already registered in the United States and the European Union. Also the results of the studies concerning the use of preoperative systemic treatment in patients with loco-regionally advanced melanomas seem to be very promising.

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Key words: melanoma, adjuvant treatment, preoperative treatment, BRAF inhibitors, MEK inhibitors, immunotherapy, anti-PD-1

Introduction

Surgical intervention is the treatment of choice in patients with melanomas. However, the prognoses of patients with melanomas at the IIC–IV stage, even after a complete resection of the lesions, is very diverse and, to a great degree, connected with a high risk of disease recurrence [1–5]. Currently, systemic adjuvant treatment after surgical intervention in the group of patients with a high risk of disease recurrence, has become the treatment standard. A novel approach to the treatment of melanomas with locoregional advancement are studies concerning the implementation of a systemic preoperative treatment. Given the combination of the surgical intervention and conservative treatment, the core binding standard should be the management of the disease by multi-specialist teams whose members are experienced in the diagnostics and treatment of patients with melanomas with locoregional and systemic spread.

Neoadjuvant treatment

Neoadjuvant treatment has been growing in significance in cases of borderline resectable tumours or locally advanced locoregional stage III metastases. The results of the II phase trials published in 2018–2019 point out that the use of combined preoperative treatment with BRAF and MEK inhibitors (with the presence of the *BRAF* mutation) or anti-PD-1 immunotherapy in combination with z anti-CTLA-4 treatment, leads to a response to therapy in a significant of patients whilst complete pathological remissions are connected with better prognoses.

The report of Amaria et al. [6] presents the results of neoadjuvant treatment with dabrafenib and trametinib applied in patients with resectable III and IV stage melanomas (with the exception of the metastases in the brain and bones) with the presence of the *BRAF* mutation. This treatment was carried out within II phase clinical trials with a random patient selection.

Seven patients were randomly selected for a standard surgical intervention with possible adjuvant treatment whilst 14 patients – for preoperative treatment with dabrafenib with trametinib, and then (after the resection) for an adjuvant treatment for up to one year. The trial was prematurely terminated on account of a significantly longer event-free survival (EFS) in the neo-/adjuvant arm in comparison with the standard treatment arm. After a follow-up period with the median follow-up of 18.6 months, the rate of patients who survived in the arm which underwent neo-/adjuvant treatment (71%; 10/14) was significantly larger than the rate of patients surviving in the group treated according to standard methods (0). The median EFS was 19.7 months *vs*. 29 months respectively ($p < 0.001$). The neo-/adjuvant treatment with dabrafenib with trametinib was well tolerated. A radical surgical intervention in this group was performed in 12 patients and in 7 cases (58%) a complete pathological response was observed, which also gave better prognoses.

Similar results were obtained in the II phase trial, NeoCombi [7], in which patients in the IIB–C stage with confirmed *BRAF* mutation, received dabrafenib with trametinib for 12 weeks before the resection of metastases and 40 weeks after the surgery. The study comprised 35 patients and in 30 of them (86%), the response to the preoperative treatment, according to the RECIST criteria, was observed, whilst in 17patients (49%) a pathological complete response (pCR) was found. The rate of the 2-year progression-free survival was 43.4%, with better results observed in the group of patients with the complete pathological response.

Two other studies evaluated the use of preoperative immunotherapy. The first of them [8] concerned the application of preoperative nivolumab (up to 4 doses) in comparison with ipilimumab together with nivolumab (up to 3 doses) in 23 patients with resectable stage III or IV melanomas. The treatment with ipilimumab with nivolumab was connected with a high response rate (73%; pCR 45%), yet with significant toxicity (73% adverse events [AE] with grade 3.), whilst monotherapy with nivolumab gave much fewer responses (25%, pCR 25%), yet its toxicity was low (8% AE in stage 3.). The latter study, [9] OpACIN-neo, evaluated the best regime with the use of nivolumab in connection with ipilimumab with the use of randomisation:

- in group A: 2 ipilimumab cycles 3 mg/kg body weight, plus nivolumab 1 mg/kg body weight every 3 weeks;
- in group B: 2 ipilimumab cycles 1 mg/kg body weight, plus nivolumab 3 mg/kg body weight, every 3 weeks;
- in group C: 2 ipilimumab cycles 3 mg/kg body weight, every 3 weeks and then 2 ipilimumab cycles 3 mg/kg body weight, every 2 weeks.

The study comprised 86 patients in stage III of the disease with clinically confirmed metastases in regional lymph nodes. Within the first 12 weeks, immune-related adverse events (irAE), grade 3–4 were found in 40% of patients in group A, 20% in group B, and 50% in group C. Objective radiological response to treatment was obtained in 63% of patients in group A, 57% in group B, and 35% in group C. A pathological response was found in a larger rate of patients than a radiological response. In 57% of patients in group B, pCR was confirmed. None of these groups obtained the median event-free survival (EFS) or median relapse free survival (RFS).

During the follow-up period, symptoms of a relapse were observed in none of the patients. The B regimen seems to be the most preferred option for further studies.

Moreover, in some patients neoadjuvant treatment seems to be more efficient than adjuvant therapy (which might be connected with the activity of the immune system). What is more, this is a short lasting therapy and, as such is cost-effective. This type of treatment allows also for a better prognostic/predictive evaluation and personalisation of the follow-up examinations after therapy; in particular no complete histopathological response was obtained and a patient might require adjuvant treatment (e.g. radiotherapy or targeted treatment with *BRAF* and *MEK* inhibitors after preoperative immunotherapy). In the entire studied patient population group, within the neoadjuvant treatment (table I), the rate of complete pathological remissions was 41% (38% after immunotherapy and 47% after molecularly targeted treatment). This strategy, however, requires further research with the participation of randomly selected patients and a comparison with postoperative adjuvant treatment.

Table I. The most important clinical trial concerning neoadjuvant treatment of melanoma with locoregional spread

Clinical trial	Treatment regime	n	pCR (%)	Median RFS (months)	Median follow-up (months)
Amaria *Lancet Oncol* 2018 [6]	Dabrafenib/trametinib	21	58	19.7	18.6
Long *Lancet Oncol* 2019 [7]	Dabrafenib/trametinib	35	49	23.0	27.0
Blank *Nat Med* 2018 [10]	Ipilimumab + nivolumab	10	33	NR	32
Amaria *Nat Med* 2018 [8]	Nivolumab/ipilimumab + nivolumab	12 11	25 45	NR NR	20
Huang *Nat Med* 2019 [11]	Pembrolizumab	30	19	NR	18
Rozeman *Lancet Oncol* 2019 [9]	Ipilimumab + nivolumab	86	57	NR	8.3

pCR – complete remission in histopathological assessment, RFS – recurrence free survival, NR – not reached

Adjuvant radiotherapy

In individualised cases, after surgical treatment of patients with high-risk melanomas, it is possible to use adjuvant radiotherapy (RTH) – the dosage pattern comprises a hypofractionation at 3–8 Gy/fraction or conventional fractionation depending on the location of the lesions. Indications for adjuvant RTH after resection of the primary tumour may comprise:

- a diagnosis of the desmoplastic melanoma resected with narrow margins,
- the presence of "positive" surgical margins (especially after the resection of local relapse) with the lack of any possibility of radicalisation of surgical intervention,
- the presence of satellite foci,
- sever neurotropism, or:
- location in the area of head and neck (note: RTH is the ole method of treatment and may be applied in the cases extensive lentigo malignant melanoma (LMM).

In the case of the resection of local lesions and lymphadenectomy in the case of metastases in regional lymph nodes, the indications for adjuvant RTH may comprise:

- the presence of extracapsular infiltration of the tumour,
- the involvement of ≥4 lymph nodes (IIIC stage),
- metastases diameter >3 cm,
- metastases were found in the lymph nodes of the neck (from 2 lymph nodes involved with metastases or in the case of metastases size of at least 2 cm),
- a relapse after a previous resection [1, 2, 4, 12].

The results of one completed study with a random selection of patients in which the value of the adjuvant radiotherapy was evaluated (48 Gy in 20 fractions) after a lymphadenectomy in the case of a high risk of melanoma relapse, confirmed the improvement of the local control after the radiation therapy. At the same time, no effect from radiotherapy on the overall survival was observed. That said, an increase in the frequency of distant locoregional complications and a deterioration of the patient's quality of life were observed. These results suggest that the use of adjuvant radiotherapy should be limited [13, 14]. It must also be stressed that there are no indications for RTH undertaken after the completion of a lymphadenectomy (CLND) resulting from the positive result of a sentinel node biopsy.

Systemic adjuvant therapy

Currently, systemic adjuvant therapy is a standard treatment in clinical practice for patients after a radical resection of primary lesions and a lymphadenectomy, whilst adjuvant radiotherapy might be considered solely in the strictly defined cases described above. The results of recently published clinical trials point to an improvement in therapy results through the use of immunotherapy with immune system checkpoint inhibitors as well as combined treatment with BRAF and MEK inhibitors [1–4].

Interferon

For many years, apart from interferon (IFN), no other agents had been effective in the treatment of high risk skin melanomas. Interferon (mainly alfa-2b IFN only in monotherapy) used for adjuvant treatment of patients with melanomas (for a highly selected group) leads to (in a repetitive way) prolongation of the relapse-free survival (RFS) in the majority of patients (table I) [4, 15–19]. However, evidence for the improvement of overall survival (OS) as a result of the use of IFN is much weaker and more controversial. In 10 out of 17 evaluated studies, an improvement in RFS was observed, and the recent results of meta-analysis point to a decrease of the risk of relapse by 17–18% (relative risk [hazard ratio, HR]: 0.82–0.83; $p < 0.0001$) after the use of IFN in adjuvant treatment. Evidence for an improvement in OS comes mostly from meta-analyses and translates into an OS improvement of about 3% within 5 years within the entire patient group. The use of IFN in adjuvant treatment in all patients with high risk melanomas is therefore not justified (especially given a significant toxicity of the treatment) and thus becomes only some option in selected patients.

On the basis of the positive results of one of the three studies carried out by the Eastern Cooperative Oncology Group (ECOG): ECOG 1684, Interferon alfa-2b (IFN α-2b) administered in high doses was registered in the United States and the European Union for the treatment of melanomas in IIB–III stage, whilst in small doses it was registered in the European Union for patients in stage II of the disease. The basis for the registration was the prolongation of the overall survival in a 7-year follow-up period, which, however, was not confirmed after a longer period of time (12 years). The results of the metanalyses show that the basic group for which the adjuvant treatment with IFN is beneficial are patients with an ulcerated primary focus of melanoma, in particular those with metastases which are not clinically overt (former terminology: micro-metastases) and not with clinically overt metastases observed in the enlarged lymph nodes (former terminology: macro-metastases) [17, 18].

Currently, the results of the 18081 study of the European Organisation for Research and Treatment of Cancer are expected, concerning the evaluation of the use of the pegylated IFN form in the treatment of patients after resection of a primary skin melanoma with ulceration without metastases in the regional lymph nodes (the study recruitment was discontinued).

The most frequent adverse effects of IFN comprise of flu-like symptoms, fever, fatigue, neutropenia, hepatoxicity and depression. Some part of the IFN toxicity profile changes within the course of treatment. Together with the length of the treatment, the flu-like symptoms recede whilst others reported adverse events remaining unchanged or even increasing with the length of treatment (mainly: fatigue, anorexia, symptoms of depression/anxiety).

Immunotherapy with immune system checkpoint inhibitors

In 2015 the results of the study became available concerning the use of adjuvant therapy with anti-CTLA-4 antibody (ipilimumab) after a lymphadenectomy due to metastases in the regional lymph nodes (III stage). 951 patients were enrolled in the study, and they were randomised to the group with a high dose of ipilimumab: 10 mg/kg of body mass for 3 weeks and then every 3 months up to 3 years (n = 476) or to the placebo group (n = 476). With the median follow-up period of 2.7 years, 234 events in relation to the RFS in the group with ipilimumab were observed in comparison with 294 events in the group with placebo; the median RFS was 26.1 months versus 17.1 months, respectively (p = 0.0013). The improvement of RFS concerned both the patients with macro-, and micro-metastases (definitions according to the TNM classification binding at that time) in the lymph nodes, and the effect of the adjuvant treatment was more significant with the ulceration of primary focus. In the group treated with ipilimumab, adverse effects occurred in 54% patients with 3–4 toxicity grade in comparison with 25% of patients receiving the placebo. On account of the complications connected with the administration of ipilimumab, 5 patients (1%) died. Adverse effects led to permanent discontinuation of the therapy in 52% patients who had started treatment with ipilimumab [20].

The median follow-up period in this study was 5.3 years. The results pointed to a significant improvement after adjuvant therapy with high doses of ipilimumab, both with regards to the relapse free survival period as well as the distant metastasis free survival and OS. The rate of the 5-year OS in the group receiving ipilimumab was 65.4% in comparison with 54.4% in the group with the placebo, the hazard ratio (HR) for death was z 0.72; 95.1% and the confidence interval (CI) 0.58–0.88; p = 0.001) [21].

The preliminary results of another study (E1609) showed a similar efficacy of a lower dose of ipilimumab (3 mg/kg of body mass) with lower toxicity. The EORTC 18071 study resulted in the registration of ipilimumab in the United States in the adjuvant treatment of patients with melanomas after a lymphadenectomy on account of the metastases in regional lymph nodes. However, the practical application of this therapy is limited because of its high toxicity and the fact that the trials with the anti-PD-1 antibodies (nivolumab and pembrolizumab) and kinase inhibitors gave more beneficial results (table II).

The study CheckMate 238 with a random selection of patients in clinical IIIB, IIIC and IV stages after resection of metastases, showed that after one year of treatment with po nivolumab, recurrence-free survival improved by 10% in comparison to treatment with ipilimumab; nivolumab showed a lower toxicity than ipilimumab (18-month RFS: 65% *vs.* 53%) [22]. This was the only study where patients after the resection of distant metastases were included. Moreover, there was an improvement in the distant metastases free survival (DMFS): HR 0.73). Adverse events, in the 3 or 4 grade, connected with the treatment were observed in 14.4% of patients receiving nivolumab in comparison with 45.9% in the group treated with ipilimumab [23]. The update of the data from 2018 with the longer follow-up period confirmed the beneficial effects of nivolumab in the year-long adjuvant treatment irrespective of the PD-L1 expression status and BRAF mutation in reference to RFS (HR 0.66) and DMFS (HR 0.76) [17]. Nivolumab is currently registered for adjuvant treatment in the United States and the European Union.

The results of the Keynote-054/EORTC 1325 study with the participation of 1019 patients point to a decrease in the risk of recurrence (HR for RFS 0.57) and DMFS after one year of adjuvant treatment with pembrolizumab in comparison with the placebo in the group of patients in stage III, characterised

Table II. The summary of the most recent clinical studies concerning adjuvant treatment after the resection of melanoma with high recurrence risk

	EORTC 18071 ipilimumab *vs.* placebo	**BRIM-8 vemurafenib *vs.* placebo**	**COMBI-AD dabrafenib + trametinib *vs.* placebo**	**CheckMate 238 IPI *vs.* NIVO**	**EORTC 1325/ /Keynote 054 pembrolizumab *vs.* placebo**
Author	Eggermont 2015 [21] Eggermont 2016 [22]	Maio 2018 [29]	Long 2017 [26] Hauschild 2018 [27]	Weber 2017 [22, 23]	Eggermont 2018 [24]
Population	IIIA (>1 mm), IIIB, IIIC	IIC, IIIA, IIIB, IIIC	IIIA (>1 mm), IIIB, IIIC	IIIB, IIIC, IV	IIIA (>1 mm), IIIB, IIIC
BRAF mutation	?	100%	100%	41%/43%	
RFS	41% *vs.* 30% (5 years)	82% *vs.* 63% (12 months); 62% *vs.* 53% (24 months); 79% *vs.* 58% (12 months); 46% *vs.* 47% (24 months) IIIC; 84% *vs.* 66% (12 months); 72% *vs.* 56% (24 months) IIC–IIIB	67% *vs.* 44% (2 years) HR = 0,47; 58% *vs.* 39% (3 years)	66% *vs.* 53% (18 months); 62.6% *vs.* 50.2% (24 months) HR 0.66 HR 0.65	HR 0.57; difference after 18 months 18.2%: 71.4% *vs.* 53.2%
OS	65% *vs.* 54% (5 years) HR = 0.72	BD	91% *vs.* 83% (2 years); 86% *vs.* 77% (3 years) HR = 0.57	BD	

OS – overall survival , RFS – recurrence free survival, BD – no data

with a higher risk (i.e. stage IIIA with the micro-metastasis size >1 mm, IIIB and IIIC) [24]. A re-classification with reference to a new classification of stage III according to AJCC (eighth edition) confirms the benefits with respect to RFS (test for interaction: p = 0.68) after one year of treatment with pembrolizumab in comparison with the placebo (excluding IIIA stage), respectively:

- IIIB stage (79.0% *vs.* 65.5%; HR 0.59 [99% CI 0.35–0.99]),
- IIIC stage (73.6% *vs.* 53.9%; HR 0.48 [99% CI 0.33–0.70]),
- IIID stage (50.0% *vs.* 33.3%; HR 0.69 [0.24–2.00]) [25].

Currently there is an ongoing study comparing the use of nivolumab and the combination of nivolumab with ipilimumab in adjuvant treatment (CheckMate 915).

Molecularly targeted therapy

Adjuvant therapy with the use of dabrafenib with trametinib in the group of high risk stage III patients with *BRAF* mutation, showed an improvement of RFS (HR 0.47), DMFS (HR 0.51; 91% *vs.* 70% after one year, 77% *vs.* 60% after 2 year and 71% *vs.* 57% after 3 years) and OS (HR 0.57) in comparison with the placebo. In this study (COMBI-AD), dabrafenib in combination with trametinib were used for a year in comparison with placebo (IIIA stage with the metastasis size >1 mm, IIIB/C) [26]. The benefits in treatment with dabrafenib in combination with trametinib were observed in all the analysed subgroups. The update of the data from the 4-year follow-up periods confirm the benefits of treatment with dabrafenib in combination with trametinib (RFS: 54%; HR: 0.49; DFS: 67%; HR: 0.53) [27]. Moreover, the model evaluating the cure rate of patients treated with adjuvant therapy in this case makes up as much as 17% [27]. The safety profile of dabrafenib in combination with trametinib was compliant with the profile observed in the study comprising patients with melanoma in stage IV, but the entire treatment was relatively well tolerated (although 26% patients discontinued treatment) [28].

Formally, a "positive" clinical study BRIM-8 [29] also concerned the application of vemurafenib in monotherapy in adjuvant treatment (in comparison with the placebo). This treatment was applied in stage IIC–III patients treated for melanoma after resection (this has so far been the only study comprising patients with stage II melanoma). The median disease-free survival (DFS) was 23.1 months in the group treated with vemurafenib, in comparison with 15.4 months in the group with the placebo (HR 0.8; p = 0.026), yet this effect was limited solely to the subgroup with tumour stage IIC–IIIA–IIIB, and was not observed in patients with more advanced melanomas (IIIC). At the same time, we can observe from the current experiments carried out with patients with metastatic melanomas with the BRAF mutation , that monotherapy with BRAF inhibitors is not the optimal treatment method in comparison with the combined treatment with BRAF and MEK inhibitors for these patients.

Conclusions

The summary of the results of systemic adjuvant treatment with the use of immunotherapy after the resection of high-risk melanoma is presented in table II. Other methods of immunotherapy (e.g. interleukin 2), vaccinations or cytotoxic medication do not have any application in post-operative adjuvant treatment [1, 4, 5, 30].

To sum up, in accordance with Polish and American recommendations [2, 4, 31] adjuvant treatment with anti-PD-1 immunotherapy with (nivolumab or pembrolizumab) or combined treatment BRAF and MEK inhibitors (dabrafenib in combination with trametinib for the patient population with the *BRAF* mutation) has become a new therapeutic standard for patients after resection of melanomas with a high recurrence risk (resection stages IIIA–IV). This, in turn, leads to the fact that the cases of all patients with melanomas in stages from IIIA to IV should be discussed at multi-specialist team meetings so as to guarantee patients optimal, modern, and as effective as possible treatment options. Additionally, it must be remembered that high risk melanomas should be included into prospective clinical trials concerning new methods of adjuvant treatment.

Conflict of interests: Piotr Rutkowski has received honorariums for lectures and Advisory Board from Novartis, BMS, MSD, Roche, Amgen, Pierre Fabre.

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