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Review article

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Management of melanoma metastases in the brain

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The basic principle for the diagnosis of melanoma metastases in the brain should be the management of multidisciplinary teams including at least a neurosurgeon, radiotherapist and clinical oncologist experienced in the treatment of melanoma and melanoma metastases in the CNS. Detection of brain lesions is associated with poor prognosis; metastases in the brain are the cause of death in 20–50% patients, and symptomatic tumours are a direct cause of death in about 90% patients. Treatment of melanoma with CNS metastases may include local management and/or systemic and symptomatic treatment. In the last 5 years, 10 new advanced melanoma drugs have been registered in Europe. Two-drug therapy anti-PD-1 and anti-CTLA-4 (nivolumab with ipilimumab) is the treatment of choice for asymptomatic melanoma metastases in the brain, while in the presence of *BRAF* mutations and asymptomatic metastases systemic treatment with BRAFi and MEKi may be the first-choice treatment.

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Introduction

In terms of the frequency of metastases in the brain, melanoma is the third most common malignant tumour after breast and lung cancer. It is estimated that in the course of advanced melanoma in about 50–60% patients the disease will spread to the brain (including about 75% patients with multiple metastases, often initially asymptomatic). In autopsy about 75% of patients have metastases in the brain. At the moment of diagnosis of melanoma, 7% of patients have metastases in the brain. In 3% of patients with diagnosed metastatic lesions in the brain, the primary lesion cannot be found. It should be noted that only in 8–46% melanoma patients metastatic tumours in the brain are found *in vivo*, and in 94% of them they are the direct cause of death.

In the latest classification of melanoma severity according to American Joint Committee on Cancer (AJCC; eighth edition) metastases in the brain were distinguished as a separate, last category in the fourth stage of melanoma severity – M1d. [1]. The risk of metastases in the brain increases with the grade of melanoma [2]. Currently, there are no predictive possibilities to determine the risk of metastases in the central nervous system (CNS) in patients with melanoma. However, it is known that some factors contribute to a higher risk of metastases in the CNS (primary lesion in the head and neck, increased activity of lactate dehydrogenase (LDH), ulceration in the primary lesion, mutations in the *BRAF, NRAS* and *PTEN* genes) [3].

The occurrence of brain lesions is associated with poor prognosis. Metastases in this part of the CNS contribute to death in 20–50% patients and symptomatic tumours are the direct cause of death in about 90% patients. Historical data show that the overall survival (OS) median after the diagnosis of brain metastasis is within 5–7 months, whereas in patients with symptoms of the disease treated with whole brain radiotherapy (WBRT), which is currently rarely used, the OS median

was 2–5 months. In patients undergoing surgical treatment or stereotactic radiosurgery (SRS)/radiosurgery, the median overall survival was twice as long [4].

The aim of this paper is to present multidisciplinary guidelines for diagnostic and therapeutic management in patients with melanoma with brain metastases, as it is currently the greatest challenge in the care of advanced stage melanoma.

New therapies introduced into everyday clinical practice have made the current management of metastatic melanoma little in common with clinical practice 5 years ago. More and more often metastases in the brain are diagnosed before their symptoms appear, after routine brain imaging (magnetic resonance imaging – MRI and/or computed tomography – CT) during the follow-up or qualification of the patient for systemic treatment. Advanced techniques of stereotactic radiotherapy play a fundamental role in local treatment. In the last 5 years 10 new drugs for advanced melanoma therapy have been registered in Europe: vemurafenib, dabrafenib, trametinib, cobimetinib, binimetinib, encorafenib, ipilimumab, nivolumab, pembrolizumab and talimogen laherparepvec (T-VEC). In Poland, 7 new drugs are currently available under drug programmes: vemurafenib, cobimetinib, dabrafenib, trametinib, ipilimumab, pembrolizumab and nivolumab. For both pembrolizumab/nivolumab and combined therapy with BRAF (BRAFi) and MEK (MEKi) inhibitors, in the whole group of patients with metastatic melanoma with the presence of *BRAF* mutation, the median OS based on clinical data is now about 2 years (i.e. about 4 times longer than 5 years ago). Perhaps the best results can be achieved with dual-drug immunotherapy (anti-CTLA-4 and anti-PD-1), as shown by the preliminary results of studies, or other combined therapies (e.g. T-VEC + pembrolizumab) or even iBRAFi, MEKi with anti-PD-1 or anti-PD-L1. Therefore, whenever metastases in the brain are confirmed, it is necessary to investigate the presence of *BRAF* gene mutation in the fixed material (if this has not been previously evaluated) [5, 6].

The basic and post-metastatic management of melanoma in the brain should be carried out in multidisciplinary teams, whose members have experience in the diagnosis and treatment of melanoma. Such a team should include at least: neurosurgeon, radiotherapist and clinical oncologist [7].

Diagnostics

Objective and subjective symptoms of CNS metastases may be subtle and difficult to recognize. They depend, among other things, on the number, size and location of metastases. Metastases are most often formed in the telencephalon, then (about 15% of them), are located in the cerebellum and (about 5%) in the brain stem. The most common symptoms of these lesions are:

- headaches, sometimes accompanied by nausea and/or vomiting,
- epileptic seizures,
- speech, comprehension and vision disturbances,
- numbness,
- mobility disorders.

The occurrence of clinical symptoms of metastases in the CNS is associated with worse treatment outcome. Melanoma patients in stage I and II are less likely to develop metastases in the CNS than patients in stage III and IV patients [8]. In younger patients the risk of late metastases in CNS in case of thicker primary lesions is higher [9]. Based on data from retrospective analysis carried out in a large multi-centre S0008 study, the risk of metastases in the CNS in patients with melanoma at the stage of IIIB and IIIC is 15% – they were found mainly during the first 3 years after surgery[10]. The time from the treatment of the primary lesion can be relatively long and can be as long as 3–4 years (median) [11].

Therefore, in patients with melanoma at III and IV stage of advancement, it is important to detect metastases in CNS on the basis of control imaging tests, despite the absence of clinical symptoms. Performing MRI of CNS during the evaluation of disease progression after the diagnosis of melanoma in the fourth stage should be the standard of management. In patients with melanoma at the stage of IIIC and higher without tumour symptoms, CT or MRI of the CNS should be considered [6]. In the case of patients with objective and/or subjective symptoms, even of minor severity, which indicate the possibility of CNS lesions, MRI should be performed [12]. It is the most sensitive in terms of metastasis detection in CNS and has an advantage over contrasting CT. Unfortunately, MRI is less accessible and more expensive, so it can be considered a necessary complementary study in patients:

- with confirmed CNS metastases – to obtain the information necessary to determine the further course of action (number and/or location of lesions) and
- with clinical symptoms with no change in contrasting CT [13].

It should be emphasized that metastases of melanoma in the CNS are characterized by a tendency to occur in the plural and a tendency to bleed [14].

Therapeutic management

The therapeutic management depends on the clinical situation and includes systemic, local (radiotherapy/SRS and/or surgery) or symptomatic treatment. In the treatment of melanoma metastases in the CNS, apart from clinical symptoms, numerous parameters related to the disease and the patients themselves play an important role, such as:

- number, size and location of metastases,
- presence and control of lesions outside the CNS,
- previous treatment of melanoma and its outcome,
- the presence of a mutation in the *BRAF* gene,
- the patient's general condition, his or her age,
- comorbidities and their treatment.

In the symptomatic treatment of melanoma metastases in the CNS, anti-swelling drugs are used, mainly glucocorti-

costeroids, but also diuretics (loop diuretics, mannitol). In the event of an epileptic seizure, antiepileptic treatment should be instituted, bearing in mind interactions with other drugs used in the patient, including glucocorticosteroids.

Tables I and II summarize two prognostic scales used in patients with CNS metastases, where the recursive partitioning analysis (RPA) scale refers to all neoplasms and the diagnosis-specific graded prognostic assessment (DS-GPA) scale to melanoma patients only.

It should be remembered, however, that these scales were developed before the introduction of new systemic therapies for the treatment of generalised melanoma. Updated scales also include the status of *BRAF* gene mutation and the presence of metastases outside the brain.

The pattern of management in patients with melanoma with CNS metastases is presented in figure 2.

Local treatment of melanoma metastases in the brain

In patients with symptomatic metastatic melanoma lesions in the brain, the expected survival without treatment is 2–3 months, and only 13% of OS patients will survive longer than one year (better prognosis in patients under 65 years of age and with Karnofsky Performance Scale (KPS) >70 points). Prognosis is affected by the removal or irradiation of all metastatic lesions. Leaving one of several lesions causes the prognosis to be the same as in the absence of treatment [16].

Table I. RPA (recursive partitioning analysis; n = 1200) [15]

	Class I	Class II	Class III
KPS	≥70	≥70	<70
Primary lesion	Controlled	Active	Active
Age	<65	65	Any
Extracranial disease	No	Present	Present
Incidence	15%	65%	20%
Median OS (months)	7.1	4.2	2.3

Table II. Prognostic assessment of the survival of melanoma patients with brain metastases – DS-GPA scale (diagnosis-specific graded prognostic assessment) [16]

KPS (points)	<70	70–80	90-100
Number of metastases within the CNS	3	2–3	1
Points	0	1	2

Division based on the sum of the number of points awarded for KPS and the number of metastases (including the patient's age: >60 years – 0, 50–60 years – 0.5 and <50 years – 1.0)

DS-GPA	0–1.0	1.5–2.0	2.5–3.0	3.5–4.0
Median OS (months)	3.4	4.7	8.8	13.2

The median survival rate of all patients with melanoma was 6.74 months (range 3.38–13.32 months; n = 481)

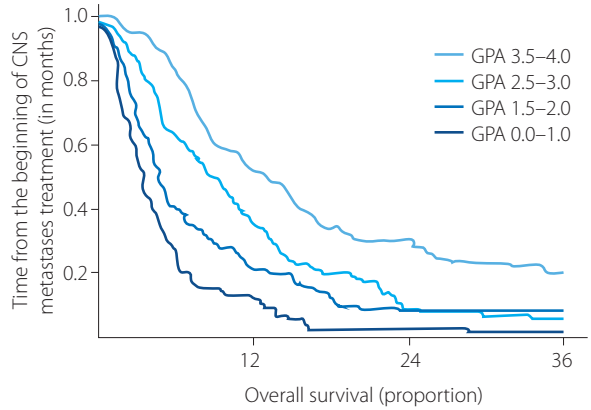


Figure 1. Kaplan-Meier survival curves for individual groups on the GPA scale [16]

There are still no clear predictive factors for the occurrence of melanoma metastases in the CNS. It is known, however, that certain factors are associated with increased risk. These include, but are not limited to:

- primary lesion within the head and neck,
- increased LDH activity,
- ulceration in the primary lesion,
- molecular changes in *BRAF, NRAS* and *PTEN* [3].

In patients with metastases in the brain, mutations in the *BRAF* gene occur in 24–58% cases and in 23% in the *NRAS* gene.

Surgical treatment

Eligibility criteria for surgical treatment of melanoma metastases in the brain (Evidence Based Medicine [EBM], 2010, level 1):

- newly discovered, single lesions up to 4,
- the size of the lesion prevents SRS (diameter greater than 3 cm),
- the location of the lesion is surgically accessible,
- symptomatic tumours causing:
  - neurological deficit and/or
  - increased intracranial pressure due to its volume and/or accompanying haemorrhage and/or secondary obstruction of the fluid pathways leading to hydrocephalus (lesions in the posterior cranial fossa),
- efficiency according to KPS >70, age <65 years,
- progression after prior stereotactic irradiation.

Objectives of surgical treatment:

- histological verification of the lesion,
- radical excision of all lesions, which affects OS (no justification for biopsy) – in case of multiple tumours, hybrid therapy (resection of large, surgically accessible lesions in combination with SRS for smaller tumours located in deep brain structures) is possible,
- improvement or stabilization of neurological condition (occurrence of new neurological deficits shortens OS by 4 months),
- enabling further oncological treatment,
- resection of symptomatic radionecrosis after SRS.

Radiotherapy

Stereotactic radiation therapy (radiosurgery)

Stereotactic irradiation is the delivery of a biologically high dose of radiation to a precisely defined small volume with a significant drop in the dispersed dose outside the target area. Treatment can be performed with one fractional dose (radiosurgery) or 3–5 fractions (fractionated stereotactic radiotherapy). Irradiation can be carried out with equipment designed for such treatment (Gamma Knife, Cyber Knife, EDGE), as well as with conventional linear accelerators equipped with high-resolution leaf collimators. The prescribed total dose and the choice of fractionation scheme depends on the location of metastatic lesions and their volume.

To achieve high local efficacy, a total dose should be administered that is more than 100 Gy after conversion to a biologically effective dose (BED). The efficacy of SRS in the treatment of small metastases of melanoma in the brain has been confirmed in many studies and is similar to that achieved by metastasectomy. The most important is the appropriate qualification of patients for treatment, which should be carried out in multidisciplinary teams.

The rules for qualifying for the SRS are as follows:

- the general condition of the patient: WHO 0–2,
- a single metastasis with a diameter of <3 cm,
- the number of metastases >1 where the total volume of the healthy brain irradiated with 12 Gy dose does not exceed 10 cm^3,
- no progression of changes outside the CNS or availability of potentially effective systemic treatment,
- irradiation of the postoperative bed [17, 18],
- possible local repeated irradiation after progression has been detected,
- life expectancy >6 months.

Recently, the indications for SRS have been extended; it was originally reserved for patients with no more than 3 metastases [22–24]. Ideally, the number of lesions should not exceed 5, but none of them should exceed 3 cm in diameter. However, a cautious qualification of patients who do not meet these assumptions is possible [19].

Nowadays, the number of metastases is of lesser importance and a limitation for stereotactic radiation is the volume of all lesions and the volume of the brain receiving a total dose of 12 Gy [25, 26]. It has been demonstrated that a healthy brain volume of more than 10 cm^3 receiving a 12 Gy dose is associated with a high risk of radionecrosis. In such clinical situations, reduction of the therapeutic dose or disqualification of the patient from stereotactic irradiation and qualification for WBRT should be considered, especially in the presence of multiple metastases. If properly qualified, local efficacy of SRS (no progression in irradiated volume) is achieved at 90–95% patients with melanoma [20, 21]. Moreover, in half of the patients a radiologically significant tumour response is observed [20]. The local efficacy is closely linked to the location of the lesion and its size.

Whole brain radiotherapy

Melanoma is considered to be a radiation-resistant neoplasm and sensitive only to higher fractional doses. Fractionation schemes used to irradiate the whole brain (whole brain radiotherapy, WBRT; 5 × 4 Gy, 10 × 3 Gy) do not provide a biological dose that allows for long-term control of the disease within the CNS. In addition, WBRT is associated with neurological toxicity. The deterioration of the quality of life of patients is caused mainly by cognitive dysfunction [27, 28]. Therefore, the WBRT should be reserved exclusively for patients:

- with a predicted short survival time,
- in poor general condition: WHO 3–4,
- disqualified from a surgery and SRS,
- with a large volume of neoplastic lesions within the CNS,
- with their rapid progression and in case of lack of possibility of effective systemic treatment,
- with metastases in the meninges, in good general condition.

Patients in very poor general condition (performance status: WHO 4) with symptoms of brain oedema that do not yield to anti-oedematous treatment should be disqualified from any form of radiotherapy. The management of choice is then symptomatic treatment, such as effective anti-oedema and antiepileptic management, as well as treatment of symptoms often associated with progression within the CNS.

The results of phase III study published in 2019 indicate that WBRT as a supplementary treatment after local treatment of melanoma metastases within the CNS does not improve the results of the therapy. The whole brain radiotherapy should therefore be reserved for patients disqualified from local treatment.

Systemic treatment

Systemic treatment is the basis of the management of patients with disseminated melanoma, including patients with brain metastases. Similarly as in the case of molecularly targeted therapy (BRAF and MEK inhibitors [BRAFi and MEKi]), the use of immunotherapy, including anti-CTL-A4 and anti-PD-1 drugs, significantly improves the prognosis of melanoma patients with metastases to the CNS. More and more long-term remissions are observed in patients responding to immunotherapy [29]. Depending on the previous treatment, the presence of V600 *BRAF* mutation and the patient's condition and clinical situation, appropriate systemic therapy should be implemented, in most cases supplemented by local treatment. In a situation of a few small metastases in the CNS, exclusive systemic treatment remains an option. Blood-brain barrier is not important for the activity of new drugs used in the therapy of melanoma.

Molecularly targeted therapy

The efficacy of molecularly targeted drugs (BRAF/MEK inhibitors) in patients with brain metastases of skin melanoma has been confirmed in several prospective clinical studies. The first clinical trials conducted exclusively in this group of patients evaluated the effectiveness of BRAFi used in monotherapy. In the largest study, including as many as 172 patients with asymptomatic metastases, the efficacy of dabrafenib (study phase II BREAK-MB) was assessed. The patients participating in the study were divided into two groups based on the previous local treatment due to brain metastases (without prior local treatment *vs.* progression after prior local treatment). The intracranial response rates were 39.2% and 30.8%, respectively. The median OS in both groups was more than 8 months [2]. In a similar clinical trial on the use of vemurafenib in 146 patients with skin melanoma with brain metastases (phase II trial), the intracranial response rate was 18% regardless of previous local treatment. The median OS was about 9 months [30]. If we take into account the assessment of responses by an independent review committee (IRC), the intracranial response rates in both studies were very similar (about 18%). These studies also showed a relatively high percentage of disease control (about 70–80%). This is due to the fact that in the majority of patients the reduction of metastatic lesions in the brain was observed, but only in some of them did it meet the criterion of partial response.

A difficult clinical situation is the presence of symptomatic metastases in the brain. This stage of disease is associated with particularly poor prognosis (median OS 3–4 months). The only clinical trial that included only this group of patients concerned the use of vemurafenib in monotherapy [31]. It was a study with a small number of patients: 24 patients not eligible for neurosurgery were included, after previous treatment of brain metastases and requiring the use of glucocorticosteroids to control symptoms. The percentage of intracranial responses was 16% and the median OS – 5.3 months. During treatment, a reduction in pain symptoms was observed, as well as improvement of patients' performance status, and reduction of the need for glucocorticoids. Unfortunately, the effect of the treatment was short-lived and the disease progressed rapidly.

The improvement of targeted treatment results was brought about by the combination therapy of BRAFi with MEKi. The only prospective clinical study evaluating the activity of this therapy in patients with metastases in the brain is phase II of COMBI-MB using dabrafenib and trametinib [32]. 125 patients with performance status 0–2 according to Eastern Cooperative Oncology Group (ECOG) with or without prior treatment of local metastases in the brain were enrolled to the study. The intracranial response rate was 56–59%, regardless of the previous local treatment and presence of symptomatic metastases. Longer duration of response was observed in patients with asymptomatic brain metastases. The median duration of the response was, however, considerably shorter than that observed in phase III clinical trials without the participation of patients with brain metastases (about 6 months *vs.* 12–14 months) [33–35]. No significant differences in treatment tolerance were observed. The most common side effects were fever and gastrointestinal disorders.

The results of the studies mentioned above confirm the activity of BRAFi/MEKi in patients with brain metastases. The response to treatment is rapid, and the reduction in tumour lesions occurs in the majority of patients. This is not only important for improvement of OS in this group of patients with poor prognosis, but also to improve the quality of life. This is particularly true for patients with symptomatic brain metastases. Unfortunately, the above data also indicate a short-term therapeutic effect of targeted treatment. Resistance in this group of patients appears faster than in patients without metastases in the brain. Therefore, in order to improve treatment outcome, attempts are currently being made to combine BRAFi/MEKi with other kinase inhibitors or immunotherapy. The results of BRAFi/MEKi tests in patients with melanoma with CNS metastases are presented in table III.

Radiotherapy in combination with targeted therapy

High initial BRAFi/MEKi activity in patients with melanoma with brain metastases has slightly changed the approach to the use of radiotherapy. The increasingly widespread use of SRS gives a high percentage of local disease control. However, it has not been shown to protect against further spread of the disease within the CNS and therefore, with the exception of patients with isolated brain metastases, has little effect on OS. Therefore, radiotherapy is often used only during the treatment of BRAFi/MEKi.

The data on the purposefulness of combining BRAFi drugs with simultaneous irradiation are contradictory. On the one hand, the potential benefits of such a strategy in terms of sensitisation of melanoma cells to radiotherapy after BRAFi, as described in in *vitro* studies, are pointed out [36]. On the other hand, the radiation-sensitising BRAFi action can lead to increased side effects, which has been confirmed by several described case studies of significant skin toxicity during simultaneous use of a combination of irradiation with these drugs, also WBRT. So far, a similar radiosensitizing effect has not been described after the simultaneous use of BRAFi with MEKi. There is no clear evidence of an increased risk of neurotoxicity, haemorrhage or brain radiation necrosis in the combination of targeted treatment with radiotherapy [37–39]. The combination of targeted treatment with radiosurgery to the CNS area gives fewer side effects than the combination with conventional radiotherapy. For conventional radiotherapy, the most common adverse reaction is skin toxicity (more severe with vemurafenib) [40].

Irradiation during targeted therapy increases the risk of dermatitis in degree II and III. As the severity of inflammation

Table III. Studies on the effectiveness of molecularly targeted therapy in the treatment of melanoma with metastases in the CNS

Study	Characteristics of patients	Number of patients	PFS (median, months)	OS (median, months)
Phase II study [30] (NCT01378975) vemurafenib	Previously untreated CNS metastases	90	3.7	8.9
	Previously treated, CNS metastases	56	4.0	9.6
Pilot study [31] (NCT01253564) vemurafenib	Previously treated, symptomatic metastases in CNS	24	3.9	5.3
Phase II study BREAK-MB [2] (NCT01266967) dabrafenib	CNS metastases without prior treatment	89	~4 [a]	~8 [a]
	Progression after prior local treatment	83	~4 [a]	~8 [a]
Phase II study COMBI-MB [32] (NCT02039947) dabrafenib + trametinib	Asymptomatic CNS metastases without prior local treatmentECOG PS 0–1	76	5.6	10.8
	Asymptomatic CNS metastases; prior local treatment ECOG PS 0–1	16	7.2	24.3
	Asymptomatic metastases with/without prior local treatment ECOG PS 0–1	16	4.2	10.1
	Symptomatic metastases with/without prior local treatment ECOG PS 0–2	17	5.5	11.5

[a] Median refers to patients with the presence of *BRAF* V600E mutation

depends on the irradiation dose, doses ≥4 Gy for conventional radiotherapy are not recommended. It is currently recommended to stop using BRAFi and MEKi at least 3 days before the irradiation and to re-activate the drugs at the earliest 3 days after its completion [37]. The exception is SRS for CNS, in which case a sufficient break in the use of BRAFi and MEKi before and after radiotherapy is one day.

Immunotherapy

Immunotherapy is the primary option in patients with melanoma with CNS metastases in the absence of V600 mutation in the *BRAF* gene. In patients with *BRAF* mutation, the choice of immunotherapy or treatment with BRAFi from MEKi depends on the clinical situation.

In an open-label phase II of clinical trial with ipilimumab (NCT00623766), the highest response rates were observed in asymptomatic patients who did not receive steroids. On the basis of immune related response (IRR) criteria, the median progression-free survival (PFS) of CNS lesions was 1.9 months in the asymptomatic group *vs.* 1.2 months in a group requiring glucocorticosteroids due to clinical symptoms of CNS metastases, and OS, respectively, 7.0 *vs.* 3.7 months [41]. In the CheckMate 204 (NCT02320058) study with nivolumab and ipilimumab, which enrolled patients with at least one CNS lesion, the primary endpoint was intracranial clinical benefit rate (CBR) – a complex endpoint including complete response (CR), partial response (PR) and stable disease (SD) for more than 6 months. The intracranial objective response rate (ORR) was 55% and CR was 21%. Extracranial responses were similar to those observed in the CNS, and the PFS rate at six months of treatment was 67%. The results of this study confirm that similarly to the treatment of extracranial disease, in patients with CNS metastases it is possible to obtain a similar response to the treatment of CNS lesions [41]. In 2019, updated CheckMate 2004 results from two cohorts of patients were presented. The A cohort included persons without neurological symptoms, not taking steroids (a cohort of patients with asymptomatic brain metastases), and the B cohort included persons with neurological symptoms – regardless of whether they received steroids or not. Patients from both groups received nivolumab (NIVO) at a dose of 1 mg/kg of body weight + ipilimumab (IPI) at a dose of 3 mg/kg b.w., every 3 weeks, 4 doses followed by NIVO at a dose of 3 mg/kg b.w. every 2 weeks – to the onset of disease progression or toxicity of treatment. In cohort A after the follow-up period of 20.6 months CBR amounted to 58.4%, while in cohort B after the follow-up period of 5.2 months it amounted to 22.2%. Level III and IV treatment-related adverse events were observed in 54% of patients in cohort A and 56% of patients in cohort B. Level III and IV nervous system related adverse events occurred in 7% and 17% of patients, respectively. Similarly, in the Australian ABC study (NCT02374242), in which the efficacy of nivolumab versus nivolumab plus ipilimumab in melanoma patients with brain metastases (n = 79) was investigated, the efficacy of immunotherapy was demonstrated, including the advantage of dual therapy in melanoma patients with asymptomatic brain metastases. In this study, the patients were assigned to three cohorts: cohort A (n = 36, a group of asymptomatic patients without local treatment due to brain metastases, receiving ipilimumab with nivolumab); cohort B (n = 27, group of asymptomatic patients without local treatment due to metastases to the CNS, receiving nivolumab); and cohort C (n = 16, patients after local treatment

due to brain metastases failure and symptomatic patients with brain metastases and patients with leptomeningeal disease, receiving nivolumab). Complete responses to treatment were observed in 17% of patients in cohort A, 12% in cohort B, and none in cohort C [42]. In the CheckMate 204 study and in the ABC study, grade 3 and 4 treatment-related adverse events in patients receiving dual therapy occurred in 52% and 54% of patients, respectively.

In asymptomatic patients, the efficacy and good tolerance of immunotherapy were confirmed by the clinical trials presented. The response rate for ipilimumab was 16% and for nivolumab and pembrolizumab about 20%. In the study of the combination of anti-PD-1 and anti-CTLA-4 in the group of asymptomatic patients, further significant improvement in treatment results was achieved. In patients with symptomatic metastases the clinical response rate was also significant and amounted to 16.7%. In the situation of the availability of combination therapy with anti-PD-1 plus anti-CTLA-4 (nivolumab with ipilimumab) and in the case of good performance status of the patient, this combination is the treatment of choice for asymptomatic melanoma patients with brain metastases.

The results of clinical studies with immunotherapy in patients with melanoma brain metastases are summarised in table IV.

Combination of radiotherapy with immunotherapy

There are more and more reports related to beneficial effect of combining radiotherapy with immunotherapy. The studies published so far show a significant increase in the percentage of the phenomenon called abscopal effect (response of untreated lesions to local treatment of other lesions) after radiotherapy was added to immunotherapy [46]. This is explained by local stimulation of the immune system and enhancement of the antigenic effect, where dendritic cells probably play a major role. There are many clinical trials underway in which radiotherapy and immunotherapy are combined. There are no contraindications for combining SRS/WBRT with immunotherapy, the decision should be made at a multidisciplinary meeting for each patient individually. Attention should be paid to the accompanying radiotherapy prophylactic anti-oedema treatment in the form of high doses of glucocorticoids that can reduce the efficacy of immunotherapy. According to current recommendations, the indications for the use of glucocorticosteroids in anti-oedema treatment during SRS are significantly limited.

The combination of immunotherapy or molecularly targeted therapy with SRS seems to be generally well tolerated, as demonstrated by studies and analyses conducted so far. In 2016, the results of the retrospective analysis done in the subgroup of patients participating in two prospective studies with nivolumab for unresectable or metastatic disease were published [47]. The analysis included 26 patients treated with melanoma and treated with SRS due to CNS metastases, including patients with CNS metastases diagnosed and treated with SRS within 6 months of treatment with nivolumab (before, after or during immunotherapy). A total of 73 CNS lesions were identified in these patients. The primary endpoint of the analysis was treatment tolerability, and secondary endpoints were intracranial disease control and extracranial disease

Table IV. Studies on the effectiveness of immunotherapy in the treatment of patients with melanoma with CNS metastases

Treatment	Patients	Characteristics of patients	IC DCR	IC ORR	IC DOR (months)	mPFS (months)	mOS (months)
IPI CA184–042 [41]	51 (A) 21 (B)	Asymptomatic Symptomatic	24% 10%	16% 5%	–	1.4 1.2	7.0 3.7
IPI + fotemustine NIBIT-M1 [43]	20	Asymptomatic	50%	40%	30.3	4.5	12.7
Pembrolizumab (NCT02085070) [44]	18	Untreated or progressive brain metastases	44%	22%	–	–	NR
NIWO: ABC; CA209–170 [42] (NCT02374242)	27 (B) 16 (C)	Asymptomatic, no local treatment (B) Prior treatment or symptomatic (C)	20% 19%	20% 6%	NR NR	2.5 2.3	18.5 5.1
NIWO + IPI: ABC; CA209–170	36 (A)	Asymptomatic, no local treatment (A)	57%	46%	NR	NR	NR
NIWO + IPI: CheckMate 204 [45] (NCT02320058)	75	Asymptomatic, prior treatment, ≤3 metastases	60%	55%	NR	NR	–

NR – not reached

control as well as OS. The majority of metastases were treated with single-fraction radiosurgery, only 12 CNS lesions were treated with fractionated SRS. In one patient headaches of grade 2 were observed, which disappeared after steroids were applied. No other neurological complications associated with the treatment were observed. In case of 8 CNS lesions (11%) failure of treatment in the form of increase of their volume by at least 20% was observed. Local control rates after six and 12 months were, respectively, 91% and 85%. The median OS was 12.0 months from the beginning of treatment with nivolumab and 11.8 months from SRS.

In 2017 a systematic review devoted to the evaluation of the tolerance of combined immunotherapy or molecularly targeted therapy with SRS was published. In the overview six retrospective studies and two case studies of patients treated with SRS and ipilimumab were included. Based on the analysis of these data, combination therapy with ipilimumab and SRS for intracranial lesions can be considered as a safe method of treatment [48].

New systemic treatment methods

Due to the often short-term or insufficient response to systemic treatment of melanoma patients with CNS metastases after immunotherapy or molecularly targeted therapy, attempts are now being made to combine BRAF/MEK inhibitors with other kinase inhibitors or immunotherapeutic agents. The objective is to improve treatment outcomes. One such study is the TRIDeNT study using nivolumab in combination with dabrafenib and/or trametinib, which may involve patients with metastases to the CNS and patients with melanoma with leptomeningeal metastases (NCT02910700) [49].

Monitoring patients after local treatment of CNS metastases and management in case of progression

Patients undergoing surgery or SRS should be monitored by performing a brain magnetic resonance imaging to quickly detect possible progression within the CNS. The first MRI should be performed within one month after surgery/SRS, and the next every 2–3 months. The imaging test results should be interpreted with caution, especially in patients undergoing immunotherapy due to the possibility of pseudoprogression and changes after treatment, which can be difficult to distinguish from disease progression. Metastases of melanoma in the CNS increase the risk of new metastases in the CNS, hence the need to monitor the CNS by means of MRI [6]. In about 50% of patients new metastatic lesions or progression of metastases previously treated (relapse in the tumour bed, progression after SRS/WBRT) will be detected [50]. However, these are not situations disqualifying from further therapy. In such a situation, one of the rescue methods of local treatment (surgery, SRS, WBRT) can usually be applied after the patient's case has been discussed at a multidisciplinary meeting [51–53]. After confirmation of the progression of CNS lesions after SRS or radiotherapy, while retaining the previously described eligibility criteria for neurosurgical treatment, surgical treatment remains the therapy of choice. Despite the introduction of modern neuroimaging techniques, it may be difficult to determine whether the observed progression is secondary to active neoplastic process or secondary to radionecrosis. In doubtful cases, the treatment of choice should be resection of the lesion, because apart from oncological indications, the removal of dead tissues has an antioedematous effect.

Leptomeningeal metastases

Prognosis in this group of patients is poor, the survival time usually does not exceed a few weeks. Data on the effectiveness of modern systemic treatment in the case of metastases to the meninges are limited and scientific evidence-based standards of management are lacking. Results of recently published retrospective analyses indicate that molecularly targeted therapy and immunotherapy may improve prognosis in these patients [54, 55]. A phase I clinical trial (NCT03025256) is currently being conducted using nivolumab, intravenous and intrathecal, in patients with leptomeningeal disease.

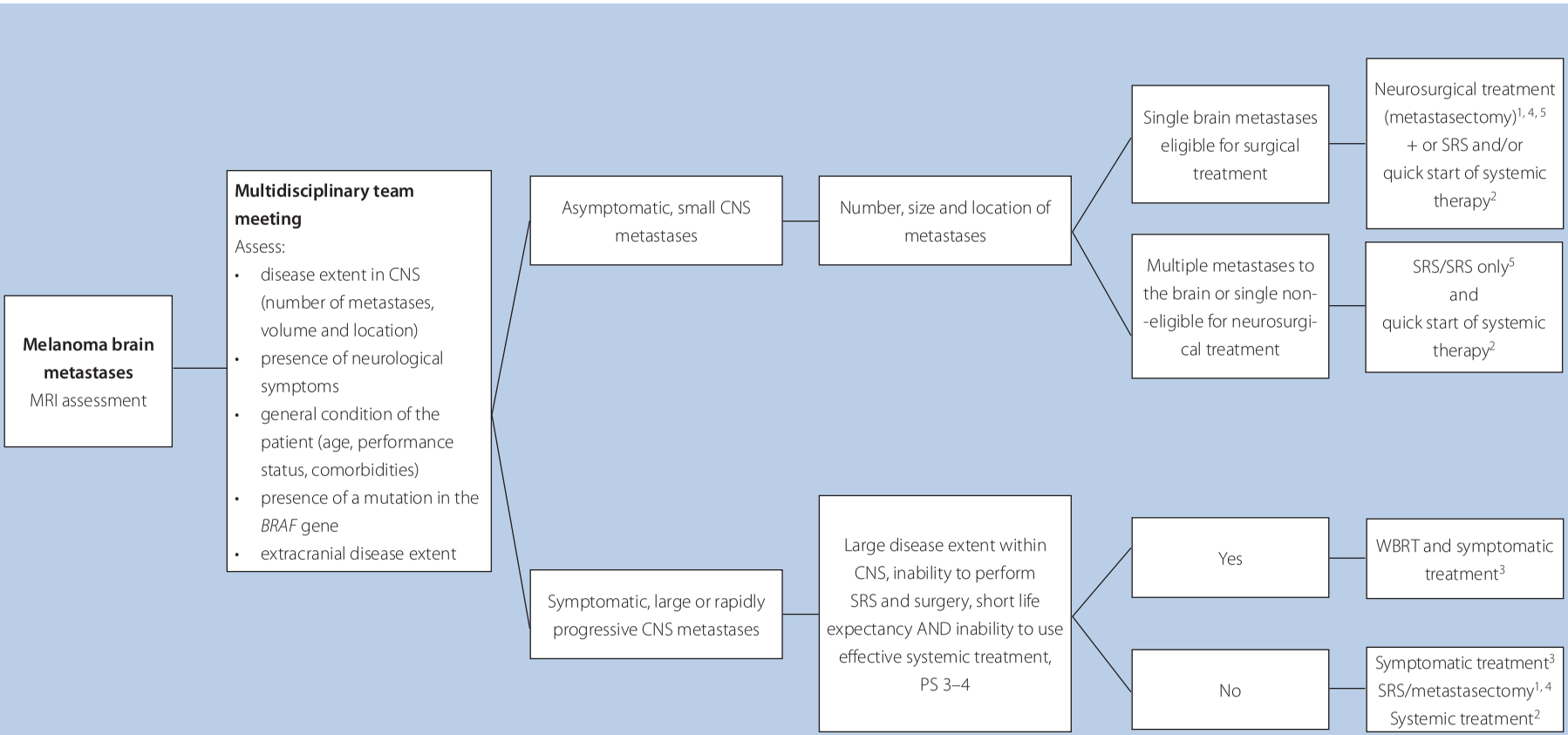
The data concerning the systemic use of IL-2 are encouraging; the 1-, 2- and 5-year survival rates in the group of 43 patients were 36%, 26% and 13% respectively. However, in view of the increased toxicity, Il-2 is not considered as a standard procedure [56].

Radiotherapy in the form of WBRT including meninges up to C2 level is a palliative treatment and should be used only in a selected group of patients (good performance status, active systemic treatment).

Summary

The basic and binding principle for the diagnosis of melanoma metastases in the brain should be the management carried within multidisciplinary teams including at least a neurosurgeon, radiotherapist and clinical oncologist experienced in the treatment of melanoma and melanoma metastases in the CNS. Predictive factors of metastases in CNS in melanoma patients have not been determined yet. Detection of brain lesions is associated with poor prognosis; metastases in the brain are the cause of death in 20–50% patients, and symptomatic tumours are a direct cause of death in about 90% patients. Historical data indicated the median OS after the diagnosis of brain metastasis was within 5–7 months. Nowadays, more and more often metastases in the brain are detected at the asymptomatic stage using routine brain imaging during patient follow-up or staging evaluation before systemic treatment.

Treatment of melanoma with CNS metastases includes, depending on the clinical situation, local and/or systemic treatment and symptomatic treatment. Advanced SRS techniques currently play a key role in local treatment. In the last 5 years, 10 new advanced melanoma drugs have been registered



CNS – central nervous system; SRS – radiosurgery; WBRT – whole brain irradiation

[1] SRS as an alternative to surgery for surgically inaccessible lesions or patients not eligible for surgical treatment.

[2] Available options include immunotherapy (nivolumab combined with ipilimumab preferred, of possible) or BRAF inhibitors with MEK inhibitors in patients with a confirmed *BRAF* mutation; simultaneous radiotherapy with BRAF inhibitors may increase the toxicity of treatment. The treatment with BRAFi + MEKi should be considered first of all in patients with the *BRAF* V600 mutation, especially when it is necessary to implement the treatment with the aim to rapidly reduce the tumour mass; in patients with brain metastases and extracranial disease the systemic treatment may be initiated during or after local treatment, bearing in mind the increased risk of simultaneous or sequential therapy with BRAFi and radiotherapy.

[3] Antioedematous and/or anti-epileptic treatment, if necessary.

[4] Adjuvant tumour bed radiosurgery is not recommended except for: leaving a tumour residue, excision of isolated CNS metastasis, without extracranial disease.

[5] In selected patients, quick start of systemic therapy and close observation of the disease within the brain should be considered (the first MR one month after the beginning of treatment, then every 2–3 months), and local intervention should be considered in the case of CNS progression.

Figure 2. Algorithm for management of patients with melanoma CNS metastases

in Europe. Thanks to the introduction of modern systemic treatment, the median OS on the basis of clinical trial data is currently about 2 years. If anti-PD-1 and anti-CTLA-4 (nivolumab with ipilimumab) are available as well as if the patient is in good condition, this is the procedure of choice for asymptomatic melanoma metastases in the brain, while in the case of *BRAF* mutations and asymptomatic metastases, systemic BRAFi and MEKi treatment can be the first-choice treatment. In every case of melanoma metastases in the brain, individual multidisciplinary assessment of the patient with neurosurgeon, radiotherapist and clinical oncologist is necessary. The summary of management in patients with melanoma with CNS metastases is presented in figure 2.

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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