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REVIEW ARTICLE

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Malignant peripheral nerve sheath tumour (MPNST)

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ABSTRACT

MPNST is a malignant neoplasm of peripheral nerves, usually arising in connection with nerve trunks of the limbs and torso. It can develop de novo or on the basis of an already existing neurofibroma. Such tumours constitute about 5% of soft tissue sarcomas. In 90%, they occur in patients in the 2–5 decade of life. The main risk factor for this cancer is type 1 neurofibromatosis (von Recklinghausen disease). The radical surgical treatment — tumour excision, within the limits of healthy tissues (wide local excision), combined with adjuvant radiotherapy, is of primary importance in the treatment of MPNST. In cases of metastatic disease, palliative chemotherapy is used, using doxorubicin or doxorubicin with ifosfamide. Clinical improvement after chemotherapy is observed in approximately 25–30% of patients. Considering the development of molecular biology research of MPNST, one can hope for development of inhibitors that show greater effectiveness than typical chemotherapy in these patients in the near future. Currently, clinical trials with pembrolizumab, nivolumab in combination with ipilimumab, pexidartinib (KIT inhibitor, CSF1R and FLT3) in combination with sirolimus, sapanisertib (TORC 1/2 inhibitor) or LOXO-195 (inhibitor of neurotrophic tyrosine kinase inhibitors NTRK type 1, 2 and 3) are performed in MNSNT patients.

Key words: malignant peripheral nerve sheath tumour, MPNST, Recklinghausen syndrome, NF1, sarcoma

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Epidemiology of MPNST

Malignant peripheral nerve sheath tumour (MPNST), previously referred to as malignant schwannoma or neurofibrosarcoma, is a rare cancer that accounts for approximately 4–5% of all sarcomas. The incidence of MPNST is approximately 0.001% in the general population, which in practice means that the incidence of MPNST is approximately 1:100,000/person-years [1, 2]. MPNST occur mainly in adults, and only 10–20% occur in patients under the age of 20 years. About half of the cases are diagnosed in patients with type 1 neurofibromatosis (Recklinghausen syndrome, NF1), where MPNST is based on plexiform neurofibroma. In this population, the incidence is 0.1% and the total risk of developing MPNST is 13–16%, compared with the incidence of 0.001% in the general population. In practice, this means that the risk of developing MPSNT in carriers of the *NF1* gene mutation is 4600 times higher than in the general population. In men who carry *NF1* mutations, the incidence of MNST increases to around 80% [2–5]. Men and women suffer with a similar frequency, although in men the disease develops earlier (on average by four years) than in women in all studied populations (Caucasian, African American, Asian). The median age of patients with sporadic MPNST ranges from 30 to 60 years, and on MPNST related to NF1 from 20 to 40 years. Metastatic disease is diagnosed in the course of treatment in 40 to 68% of patients, and likewise local recurrence in 40 to 65% of patients [2, 6, 7].

MPNSTs are most often located on the limbs (in 30% of patients) and trunk (about 50% of cases, including retroperitoneal space); however, they may also occur in other locations, including the head and neck area (about 20%). The intracranial MPNSTs not connected with cranial nerves are rather anecdotal. In turn, metastases in the course of MPNST are most often detected in the lungs, pleura, and bones [2]. About 11% of this type of

cancer develop in the previously irradiated body area. The main risk factors for developing MPNST are existing benign plexiform neurofibromas , previous radiotherapy, but also hereditary mutations (point mutation, splicing mutation, deletions, insertions, or duplications), as well as large deletions and microdeletions (< 1.5 Mb) encompassing the entire *NF1* gene together with neighbouring genes (increasing the risk by up to 25%) [1, 4].

Biology and genetics of MPNST

The genetic feature of Recklinghausen syndrome (neurofibromatosis type 1, von Recklinghausen disease) and MPNST tumours based on neurofibromas is a point mutation or other aberration resulting in the loss of the *NF1* gene function (neurofibromin 1) located on the long arm of chromosome 17 and encoding the protein with tumour suppressor function. *NF1* is a large gene, over 350 kbp in length, that includes 60 exons, which are subject to alternative splicing, leading to tissue-diverse expression of isoforms. In about half of the cases, the disease is a result of a new mutation and is not of a family nature, but is related to the father's age, because they arise as replication errors in mitosis of stem cells of spermatocytes I (spermatogonia) [8]. Loss of neurofibromin function leads to activation of Ras kinase (Rat sarcoma) followed by its effector pathways associated with malignant transformation. The degree of activation of Ras and dependent signalling pathways, as well as the sensitivity of cells to their inhibitors, is inversely proportional to the level of neurofibromin expression [9]. Activation of Ras kinase leads to the activation of two types of effector pathways: MAPK pathways (Ras/Raf/MEK/Erk) and Akt/mTOR pathways that regulate cell function, among others in response to external stimuli such as growth factors or chemokines. Both of these pathways have been described as activated in many types of sarcomas, including MPNST. It has been shown that positive IHC staining (high expression) of Akt, mTOR, and pS6RP proteins correlates with a shorter overall survival (OS) of patients diagnosed with MPNST [10]. Molecular data are preliminary circumstances for use of inhibitors of these pathways, such as mTOR inhibitors, in the treatment of patients diagnosed with MPNST. During *in vitro* research with cell line models these drugs significantly inhibited proliferation, migration, and invasiveness of MPNST cells [10]. It should be taken into account that the activation of the above-mentioned pathways is not only dependent on the lack of functional neurofibromin but may also increase as a result of activating somatic mutations of individual pathway elements or their regulators [11, 12]. Considering the complexity of dependence and the possibility of activating mutations at the same time in many genes, the use of selective inhibitors of Ras-dependent pathways may turn out to be ineffective in clinical practice, such as in the case of sorafenib as a RAS/Raf inhibitor [13]. Although single cases of effective MPNST therapy with sorafenib have been published, including metastatic disease [14], phase 2 trials of sorafenib in monotherapy (NCT00217620) and in combination with dacarbazine (S 400 mg BID and D 1000 mg/m^2 q3w) did not show a high response rate in patients with MPNST [15]. It is indicated that molecular studies, including microarrays, may be helpful in the future assessment of drug-resistance mechanisms and the selection of optimal therapy for patients with MPNST [16]. The first data showed that combinations of inhibitors of different kinases — canertinib (an EGFR, Her2, and ErbB4 inhibitor) and sorafenib — inhibit proliferation and reduce the viability of MPNST cells, but not monotherapy with sunitinib, crizotinib, or sorafenib [17]. Although the development of the canertinib molecule did not result in clinical success due to toxicity, further attempts of targeted therapy are being made according to changes in gene expression characteristic of MPNST.

Studies have shown constant phosphorylation of MEK (mitogen-activated protein kinase) and ERK (extracellular signal-adjusted kinases in MPNST tumours), which confirms the activation of the Ras/Raf/Mek/Erk pathway. Activation of MEK kinase increases invasiveness, migration, and angiogenesis, and its experimental deactivation inhibits the development of MPNST in an *in vitro* model [12, 18]. The use of the MEK inhibitor (PD0325901) resulted in the inhibition of the growth of both plexiform neurofibromas and MPNST in mice [19], and the activity of this inhibitor is potentiated by retinoids, including ATRA (all-trans retinoic acid) [20]. The efficacy of MEK inhibitors has been confirmed during *in vitro* studies also in combination with the mTOR1/2 INK128 double inhibitor [9]. This puts MEK inhibitors in the group of potential drugs in advanced forms of MPNST requiring systemic treatment. Currently, Phase 2 SARC031 (NCT03433183) is planned to assess the efficacy of the MEK inhibitor selumetinib (AZD6244) in combination with the mTOR inhibitor sirolimus for patients with MPNST.

Activation of receptor tyrosine kinases may also induce activation of the above-mentioned pathways. Among the tyrosine kinases, an important role is played by the epidermal growth factor receptor (EGFR), overexpression of which in the animal model was sufficient to transform neurofibromas in MPNST [21]. While the *NF1* mutation and the loss of neurofibromin function characterise most of the MPNST, even the loss of both NF1 alleles is not sufficient for neoplastic transformation from benign neurofibromas [22]; additional genetic disorders or signals from the tumour microenvironment are needed. Numerous genetic disorders have been described so far in MPNST — there were an average

of 18 chromosomal aberrations in them, and the most frequent ones are duplications of 7p, 8q, and 17q and loss of 9p, 11q, 13q, or 17p [23]. The most common genes that undergo mutations in the MPNST are *NF1*, *SUZ12* (polycomb repressive complex 2 subunit), *EED* (embryonic ectoderm development), and *TP53* and *CDKN2A* (cyclin dependent kinase inhibitor 2A) genes, which occur in 87.5 %, 56.1%, 32.5%, 40.3%, and 75% of cases, respectively [11]. Numerous chromosomal aberrations in MPNST have also been identified, resulting in duplication of genes such as *BIRC5*, *CCNE2*, *DAB2*, *DDX15*, *EGFR*, *DAB2*, *MSH2*, *CDK6*, *HGF*, *ITGB4*, *KCNK12*, *LAMA3*, *LOXL2*, *MET*, and *PDGFRA*; and gene deletions: *CDH1*, *GLTSCR2*, *EGR1*, *CTSB*, *GATA3*, *SULT2A1*, *GLTSCR2*, *HMMR/RHAMM*, *LICAM2*, *MMP13*, *p16/INK4a*, *RASSF2*, *NM-23H1*, and *TP53* [24]. Abnormalities of *TP53* or *SUZ12* genes occur in about 50% of MPNST cases and are not found in benign lesions, which indicates their occurrence at a later stage of tumour development. This is not the case for *CDKN2A*, which is mutated in 94% of atypical neurofibromas and 70% of MPNST and is probably involved in the transformation of neurofibromas from mild to atypical [25]. The *SPP1* gene (OPN, osteopontin) has been shown to have the greatest difference in expression between benign neurofibromas and MPNST (85-fold higher expression in MPNST), and its silencing reduces proliferation and migration of MPNST cell lines. In addition, SPP1 expression is regulated by the Wnt pathway, the role of which in progression to MPNST has also been proven [26]. Surprisingly, in contrast to other types of STS (soft tissue sarcomas), the expression of many genes coding for proteins (mRNA) and microRNA is observed in MPNST. This deregulation seems to be dependent on the inactivation of the p53 protein [27]. It is also probably caused by hypermethylation of gene promoters and activation of inhibitory microRNAs such as miR-29c [28, 29]. The gene hypermethylation pattern was also proposed as a diagnostic marker for MPNST, and the specific methylation pattern (H3K27me3) distinguishes MPNST from Schwannoma neurofibroma, nerve sheath myxoma, or ganglioneuroma. In addition, sporadic MPNST without epigenetic inactivation (hypermethylation) of the *NF1* gene in repeated pathomorphological analysis turned out to be another type of STS or cellular schwannoma [30]. Taking into account the increasing role of *SUZ12* and *EED* gene mutations, research on drugs targeting epigenetic regulators are quite promising. The HDAC (histone deacetylase 1) I/II inhibitor romidepsin (trade name: Istodax®) shows strong synergy in combination with the dual mTORC1/2 (INK128) inhibitor on the MPNST cell lines [9]. Patients with MPNST were included in the phase II trial with panobinostat (trade name: Farydak®) — a non-selective HDAC inhibitor — but this drug did not show high activity in patients with STS, as only 12.5% after six months of treatment had no disease progression [31]. At the same time, it was indicated that classical chemotherapy based on ifosfamide and doxorubicin (AI scheme with a total dose of 5 g/m^2 ifosfamide and 60 mg/m^2 doxorubicin per cycle) may be effective in patients with MPNST with loss of H3K27me3, as described above [32].

Of the genes amplifiable in MPNST, it is also worth noting topoisomerase 2a (*TOP2A*), which participates in DNA replication and is the main target of doxorubicin, widely used in the treatment of STS. *TOP2A* amplification was confirmed in a large group of patients and correlates with shorter survival and metastasis [33]. The level of *TOP2A* expression in MPNST may be up to 24 times higher than in benign neurofibromas and correlates with sensitivity to doxorubicin [34]. Determination of *TOP2A* expression is potentially useful for determining the sensitivity for, and selection of, chemotherapy.

Tumour microenvironment heterozygous for *NF1* is also involved both in the formation of neurofibromas and their malignant transformation through released growth factors, chemokines, and proinflammatory factors. This happens through a complex network of interactions between tumour cells and steep cells. Tumour cells produce a c-KIT ligand and transforming growth factor beta (TGF-B), which attract mast cells and fibroblasts, respectively. On the other hand, they release platelet-derived growth factor (PDGF) and endothelial growth factor (VEGF), which, by recruitment of fibroblasts and endothelial cells, enhance tumour growth and angiogenesis. In addition, autocrine secretion of CXCR4 and CXCL12 chemokines intensifies the progression of these changes [1]. Positive expression of the hypoxia response factor (HIF-1A) is found in about 75% of MPNST and is associated with an unfavourable prognosis [35]. In addition, MPNST is characterised by low expression of PD-L1, lack of PD-1 expression, and significant infiltration of CD8 + lymphocytes, which limits the possibility of immunotherapy [36]. Activation of the tumour microenvironment and genetic disorders occur simultaneously, and when they coexist, transformation of benign tumours in MPNST occurs.

Histopathology

MPNST are formed from neuroectodermal cells, i.e. they arise from nerve roots, plexuses, cranial nerves, and peripheral nerves. Intracranial MPNSTs arise from multipotent precursor cells of the brain parenchyma [2, 3]. The unambiguous presence of nerve elements or the presence of a tumour in patients with *NF1* mutation raises the suspicion of MPNST. However, in many cases, making the final diagnosis can be much more difficult. Analyses indicate that in no more than 39–56% of pa-

tients with MPNST the nerve from which the tumour is formed could be identified. In the case of MPNST the percentage of incorrect initial histological diagnoses is the highest among all STSs, accounting for up to 78% when the diagnosis was made outside reference centres treating sarcomas. To be qualified as MPNST, it is necessary for STS to meet one of three specific criteria: 1) the tumour has developed in the peripheral nerve, 2) the tumour has developed from the nerve sheaths of a pre-existing benign tumour (neurofibroma or others), or 3) the set of histological features of differentiated Schwann cells can be identified in the tumour [2, 37, 38]. MPNST can be in the classical spindle cell form or in the form of pleomorphic and epithelioid (epithelial) [2].

MPNSTs are characterised by a diverse morphology. On the cross-sections of MPNST tumours, there are white-and-fleshed coloured changes. In the classic form, MPNST is similar to fibrosarcoma, because it consists of spindle cell bundles. Among the most common histological features of MPNST, we can also find intertwined bands of high and low cellularity, haemangiopericytoma-like, palisadic or rosette-like cell arrangement, subendothelial accumulation of tumour cells, areas of geographical necrosis, and perineural/intraneural dissemination when associated with the nerve. However, these features are non-specific. The preparations also show the normal features of Schwann cells (nerve sheath). MPNST cells have comma-shaped or wavy cell nuclei, and virtually invisible cytoplasm, and in tumours they are often convoluted. Different types of sarcomas (synovial sarcoma, rhabdomyosarcoma, leiomyosarcoma, and diversified liposarcoma), benign mesenchymal tumours (neurofibroma), and non-ischemic tumours, especially melanoma, should be considered in differential diagnosis [2, 39].

In the case of MPNST developed on the basis of neurofibromas, it is important to distinguish between typical, atypical neurofibromas, and MPNSTs of low and high grade of malignancy. The grade is determined on the basis of the FNCLCC (Fédération Nationale des Centres de Lutte Contre Le Cancer) system, taking into account the mitotic index, degree of differentiation, and severity of necrosis. Tumours defined as atypical neurofibromas or low-grade MPNST (FNCLCC 1, WHO grade II) are sometimes categorised as ANNOUBP (atypical neurofibromatous neoplasm of uncertain biological potential) and treated as precursor changes of MPNST. They are characterised by cellular atypia, increased cellularity with little mitotic activity — < 5 mitosis per 10 high-power fields (HPF) [40]. High-grade MPNST (FNCLCC 2–3, III–IV according to WHO) are characterised by high cellular atypia, increased cellularity, presence of necrosis outbreaks, and high mitotic activity — > 10/10 HPF. In turn, tumours with mitotic activity 5–10/10 HPF may represent an intermediate category [40].

Unlike other types of sarcoma, MPNST does not have pathognomonic mutations or molecular markers (rearrangements, mutations) that would allow for a clear histopathological diagnosis, as in the case of Ewing sarcomas or malignant synovitis. A wide panel of immunohistochemical tests and stains — including IHC on S-100, Leu-7, EMA, vimentin, HMB-45, and cytokeratin — is necessary to distinguish MPNST from STS originating from other tissues. It may also be helpful to determine the *NF1* mutation from the tumour material. It is believed that in patients with confirmed *NF1* mutation, each spindle cell sarcoma should be *a priori* treated as MPNST and additional staining used for possible verification of such diagnosis [39].

A typical staining panel for differential MPNST diagnosis includes an IHC assessment of S100 protein expression (Schwann cell marker), Ki-67 (cell proliferation marker), TP53 (suppressor protein), CD34 (endothelial cell marker), and p14INK4a (inactive protein in MPNST inhibiting cell cycle) [41]. Evaluation of marker expression allows for diagnosis, but the staining pattern does not allow stratification of patients to select the appropriate treatment regimen. In some cases, it may be necessary to analyse the tumour's ultrastructure to show that the tumour originates from the nerve sheaths [1]. It should be remembered, however, that the expression of typical markers may vary depending on the degree of differentiation, e.g. S100, a characteristic Schwann cell marker, may undergo reduced expression or complete loss in undifferentiated MPNST [1]. Part of the MPNST, especially high-grade, may show positive staining of p53 proteins, which are more often positive in tumours associated with *NF1* than in sporadic MPNST [1, 42]. It is also helpful to perform additional staining with the use of muscle markers in order to confirm/rule out the rhabdomyoblastic component (MTT, malignant triton tumours), which is a negative prognostic factor (shorter time to metastases and overall survival) [43].

New markers are still being intensively sought that could help in better identification and stratification of patients diagnosed with MPNST. Although numerous potential markers have been described, occurring in most cases of MPNST, their implementation for routine diagnostics requires verification on larger cohorts of patients, in inter-centre studies, before they can be implemented in standard histopathological diagnostics. Promising results relate to markers associated with disorders in the pathway associated with remodelling of the chromatic structure of the polycomb type (PcG), i.e. polycomb repressive complex 2 (PRC2)/polycomb repressive complex 2 subunit (SUZ12), mutations found in 70% of MPNST, but not in benign plexus and atypical neurofibromas. A histological surrogate for PRC2 inac-

tivating may be the loss of methylation of lysine 27 histone H3 described above (H3K27me3). The total loss of H3K27me3 is observed in approximately 50% of MPNST and is almost absent in other tumours of similar morphology, which allows high-sensitivity (98.7%) to confirm the diagnosis of MPNST [44]. However, the specificity of the method is low and amounts to 54.2%, which does not allow the exclusion of MPNST in the case of lack or partial loss of H3K27me3 [44].

Some histopathological markers help to predict the response to some forms of treatment, but due to their presence in many types of cancer, they are not used in the diagnosis of MPNST. For this reason, they are described in the section on specific types of treatment.

Diagnostics

The tumour presence dominates in the clinical picture of MPNST, and resulting discomfort depends on its location. As the cancer develops in close connection with nerve trunks, it often causes pressure. This may result in pain and neurological symptoms peripherally to the tumour. The symptoms like sensory disturbances, paresis, and pains may uncommonly precede the appearance of a palpable tumour for many months, especially in locations that make clinical evaluation difficult, e.g. in the retroperitoneal space. Patients with MPNST usually report a rapidly growing, palpable change that can be painful or manifest in neurological disorders such as paraesthesia or weakness in muscle strength. In the case of lesions located locally or in the thorax, the diagnosis is often delayed due to non-specific symptoms and the inability to detect a tumour in a physical examination. Magnetic resonance is the best imaging method that allows assessment of the size and infiltration of the lesion regardless of location, and to plan the appropriate surgical procedure. There is no evidence of higher efficacy of open biopsy or core needle biopsy. The choice of method depends mainly on the location of the tumour and the preferences of the surgeon and patient. Fine needle aspiration has a very limited application in the diagnosis of primary change, but it is valuable in the diagnosis of local recurrence or metastasis [45]. In most cases tumour size is > 5 cm at MPNST diagnosis, and in up to 50% of patients metastases in the lymph nodes or distant metastases, usually in the lungs or liver, are present [6]. For this reason, apart from visualisation of the primary change, it is necessary to exclude the presence of metastatic lesions by means of classical imaging methods such as ultrasound, X-ray, or CT.

The majority of diagnostic difficulties concern patients with Recklinghausen syndrome; in this group of patients, assessment of the location of neurofibromas is the basis of diagnostics, especially those not available in the physical examination, as well as monitoring their possible transformation into the MPNST. The symptoms of von Recklinghausen's disease include skin colour (*café au lait* spots), numerous neurofibromas, Lisch nodules on the iris, and bone dysplasia [5, 46]. A greater risk of malignant transformation concerns tumours with a more central location (trunk, proximal limbs) and those associated with large nerve trunks. The initial assessment of the location and size of all benign lesions is particularly important due to the significant correlation between the number and total volume of neurofibromas and the risk of transformation in MPNST [47]. The best method is magnetic resonance imaging of the whole body, which, however, does not allow for a clear distinction between MPNST and benign lesions [48] and is therefore not an optimal tool for monitoring the changes. A study conducted by Ferner et al. showed that PET with fluorodeoxyglucose allows good differentiation of benign neurofibromas and MPNST. The sensitivity and specificity of PET-CT with FDG were 89% and 95%, respectively [49]. SUV_{max} does not correlate with the degree of malignancy of the MPNST tumour. The authors recommend removing tumours with $SUV_{max} > 3.5$, and for SUV_{max} between 2.5–3.5, treatment decisions should be made after critical analysis, including clinical data [49]. A meta-analysis of 13 studies showed that the sensitivity of PET-CT varies from 91% to 100%, and the specificity from 72 to 95%. The SUV_{max} cut-off point for the highest sensitivity and specificity ranges from 3.1 to 6.1. The available data do not allow determination of the unambiguous cut-off point differentiating between benign and malignant changes. Some studies indicate the possibility of reducing the rate of false positive results using delayed imaging (after 4 h) [49, 50] or normalisation of SUV_{max} to the glucose uptake by the liver or dry body mass [51, 52]. The use of PET-CT for this purpose is also recommended by Polish guidelines regarding the use of PET-CT in oncological diagnostics [52]. There are studies on other possible parameters to be evaluated in PET, i.e. MTV (metabolic tumour volume) and TLG (total lesion glycolysis), which show promising results, but there is no evidence to justify their use in routine practice [53].

Symptoms that should lead to further diagnosis in patients with Recklinghausen syndrome include: pain lasting over a month or disturbed sleep, appearance of new neurological disorders or problems with sphincter control, changes in the neurofibroma character from "soft" to "hard", and its rapid growth [54]. More intensive monitoring should also be given to patients with previous radiotherapy, an earlier MPNST diagnosis, and plexiform neurofibromas located within the shoulder plexus, lumbosacral plexus, spinal nerve roots, and in the abdominal and pelvic area, because they are associated with a more frequent transformation [49, 54].

Treatment of local disease

Neoadjuvant treatment

Similarly to other STSs, the standard of care in locally advanced MPNST is to obtain local disease control, mainly using surgical techniques [55]. In the clinical evaluation of patients, it should be taken into account that the main goal is to achieve negative surgical margins (tumour cell free), i.e. resection R0. Curing can only be achieved after radical surgical excision of the primary tumour, and in the presence of metastases also after surgical excision of metastatic lesions [3]. If there is a risk of unresectability of the tumour based on clinical data and imaging tests, neoadjuvant treatment should be considered. For this reason, preoperative treatment in the form of neoadjuvant chemo- or radiotherapy may be a reasonable management in patients with tumour size > 5 cm. Neoadjuvant treatment is also recommended in patients in whom it is important to quickly reduce tumour mass, for example a tumour pressing against the surrounding nerves and causing severe pain. Data on neoadjuvant chemotherapy in MPNST are limited to retrospective analyses of individual cases and case series. Selected studies show that in patients with primary inoperable tumours R0 resection could be achieved after chemotherapy, as in the case of analysis of paediatric patients from centres in Germany and Italy, where in 11/20 cases of MPNST complete resection after pre-operative chemotherapy was finally possible [56]. Currently there are no data from randomised trials evaluating adjuvant chemotherapy in MPNST. In mixed populations of patients with STS, meta-analysis data suggest marginal survival benefits (OS) after neoadjuvant chemotherapy [6].

Multicentre Phase II SARC006 clinical study (NCT00304083) comparing the efficacy of neoadjuvant chemotherapy using doxorubicin, etoposide and ifosfamide in patients with unresectable MPNST (Grade III–IV), in which patients received two cycles of AI chemotherapy (ifosfamide and doxorubicin) followed by two cycles of EI (etoposide and ifosfamide) chemotherapy. After four cycles patients could undergo radical treatment (radiotherapy or surgery) if they were qualified by an anaesthesiologist, and then receive two AI courses and two EI courses. After four treatment cycles, objective response rates (ORR) were achieved in nine of 37 patients, but this percentage was significantly lower in the *NF1*-mutated group than in the sporadic MPNST group (17.9% *vs*. 44.4%). Twenty-four patients achieved disease stabilisation (SD). After four cycles of chemotherapy 22 patients underwent surgery, radiotherapy, or a combination of both methods, with a radical intention. Due to the small number of patients, the study did not indicate sufficient statistical power to show differences in the obtained responses between sporadic MPNST and MPNST associated with *NF1*, but there was a tendency for worse response to chemotherapy in patients with *NF1*. In addition, this study also confirmed the role of neoadjuvant chemotherapy in patients with primary unresectable MPNST tumours [57].

The EUDRACT 2010 study — 023484-17 (NCT01710176) reports that 3 courses of anthracycline-based chemotherapy and a full dose of ifosfamide (epirubicin 120 mg/m^2 + ifosfamide 9 g/m^2), administered in neoadjuvant treatment, gives a 20% gain in RFS and OS [58]. The use of such a treatment regimen allows for a radiological (RECIST) and metabolic (PET) response, and the use of epirubicin in place of doxorubicin may be associated with a lower risk of cardiotoxicity [59]. The recently published SG-STS 1001 study showed greater efficacy of the anthracycline regimen (epirubicin 60 mg/m^2 d1, 2 plus ifosfamide 3 g/m^2 d1, 2, 3; q3w) compared to EI chemotherapy (etoposide 150 mg/m^2 d1, 2, 3 plus ifosfamide 3 g/m^2 d1, 2, 3; q3w) [60].

In the paediatric population with inoperable MPNST treated in Polish oncological centres, a good response (defined as a reduction in tumour size by over 33%) to neoadjuvant chemotherapy (vincristine, ifosfamide, dactinomycin, doxorubicin or epirubicin, etoposide, and carboplatin) was found in 47.6%. The presence of *NF1*, high expression of osteopontin, survivin, p53, and cyclin D were negative predictors of response to chemotherapy. Patients with three or more markers responded significantly worse to the treatment. These markers have not been studied so far in the adult population. Differences in chemotherapy regimens in children and adults should be taken into account, as well as a slightly different MPNST biology in these age groups. For this reason, data on the effectiveness of treatment in the paediatric population cannot be directly translated into adult populations [61]. A study is currently being conducted (NCT02180867) on the combination of pazopanib with AI chemotherapy and radiotherapy in pre-operative treatment of patients with MPNST.

Surgery

The radical surgical treatment — tumour excision — within the margins of healthy tissues (wide local excision), combined with complementary radiotherapy, is of primary importance in the treatment of neurosarcomas. Resectability of MPNST depends on tumour location. In the case of limb localisation, radical resection is possible in most patients, and sometimes it is necessary to remove the main nerve trunk (e.g. sciatic nerve). Centrally located tumours (often paraspinal, with spreading along the nerve roots towards the meningeal sac) are resectable in about 20% of patients [62]. In the case of resection R1 and R2, reoperation and/or postoperative radio- and/or chemotherapy should be considered.

Adjuvant treatment — chemotherapy

The use of adjuvant chemotherapy in patients with STS has been associated with many controversies for years. A meta-analysis of 18 randomised clinical trials in patients with locally advanced STS, not histopathologically specified, showed improvement in the control of local recurrence (OR 0.73, 95% CI 0.56–0.94, p = 0.02) and distant metastases (0.67, 95% CI 0.56–0.82, p = 0.0001) indicating a beneficial effect of adjuvant chemotherapy. In terms of overall survival, adjuvant chemotherapy with doxorubicin monotherapy did not affect OS (OR 0.84, 95% CI 0.68–1.03, p = 0.009), but in combination with ifosfamide, OS improvement was statistically significant (OR 0.56, 95% CI 0.36–0.85, p = 0.01). However, the higher toxicity of the combination of doxorubicin and ifosfamide should be considered. Furthermore, the meta-analysis included most histological types of STS but data was presented not only for MPNST [63].

It was estimated that in the case of completely resected tumours (R0) with a wide margin there is no need for postoperative treatment; however, some authors believe that adjuvant chemotherapy should be used in all cases of MPNST with a diameter of more than 5 cm [56].

Radiotherapy

It should be emphasised that radiotherapy does not improve overall survival in this group of patients, but it reduces the risk of local recurrence [64]. The lack of adjuvant radiotherapy is associated with a 4.5-fold higher risk of local recurrence (HR 4.5) [39]. A retrospective single-centre analysis of a group of 134 patients treated for MPNST showed a significant effect of factors associated with radiotherapy on the local efficacy of combination therapy. Better results in this respect were obtained in patients who received a dose higher than 60 Gy and in a subgroup of patients treated with brachytherapy or intraoperative radiotherapy as a component of perioperative treatment [65]. In the case of MPNST located in the peri-vertebral region or the base of the skull after non-radical resection or without the possibility of performing an operation, radiotherapy with the use of protons or heavy ions plays an increasingly important role; they allow a high local efficacy with relatively few side effects [66, 67]. However, the available literature data in this respect are too sparse to draw unambiguous conclusions. Treatment planning, including disc volume determination and fractionation, does not deviate from the recommendations used in perioperative treatment of soft tissue sarcomas.

Treatment of metastatic/recurrent disease

MPNST is a cancer with a high degree of malignancy with high risk of metastases. In cases of generalised disease, palliative chemotherapy is used, with doxorubicin or doxorubicin and ifosfamide. Clinical improvement after chemotherapy is observed in approximately 25–30% of patients. Considering the effectiveness of molecularly-targeted treatment of patients with gastrointestinal stromal tumours (GISTs) and fairly well-known molecular biology of MPNST, especially in patients with neurofibromatosis, one may hope to develop in the near future inhibitors that show greater than typical chemotherapy efficiency those patients. In the group of patients with MPNST, treatment gives a five-year survival ranging between 50 and 55%. Patients with sarcoma developed in the course of neurofibromatosis have a poorer prognosis. The five-year survival in this group is around 20–30%. The average disease-free survival time is also shorter in cases of MPNST developed in NF1. These patients are also characterised by a higher, understandable risk of new tumour outbreaks [68]. However, there are indications that prognosis in patients with MPNST developed in the course of NF1 is gradually improving, and the results are close to those achieved in patients with sporadic sarcoma [69].

Treatment of relapse and metastatic disease

Surgery

Surgical treatment is also used in the treatment of recurrent disease — both for recurrences and single distant metastases. The relapse re-incidence is lower than in primary tumours, and in some patients radical oncology can be obtained by performing limb amputation. Due to the fact that MPNST is often formed in connection with large nerve trunks, even the operation with limb saving is often associated with the formation of large functional defects.

In the treatment of patients with MPNST, it is important to obtain negative surgical margins (R0), because many analyses have shown significantly shorter survival in patients with positive operating margins (R1/2) [39, 70–72]. In a French study, patients with R0 resection had almost twice the median disease-free survival as patients after resection of R1 or R2 (47.8 *vs.* 24.4 *vs.* 24.4 months, respectively) and presented significantly greater percentages of overall survivals after eight years (57.1% *vs*. 48.4% *vs.* 25.5%, respectively) [70]. Positive operational margins are also associated with an almost six-fold greater risk of local recurrence [73] and distant metastases [74].

Palliative chemotherapy

An analysis of 12 clinical trials conducted by EORTC in patients with advanced soft tissue sarcoma (STS) showed no difference in response rate (21 *vs*. 22%,

Table 1. Median PFS and 1-year overall survival in patients with advanced MPNST depending on the regimen of first-line chemotherapy — analysis of 12 EORTC clinical trials [75]

Chemotherapy regimen	PFS	1-year overall survival
Anthracycline monotherapy	17 (13.7–20.43)	14.8%
Ifosfamide monotherapy	9.4 (7.1–17.0)	3.85%
Doxorubicin + ifosfamide (AI)	26.9 (22.4–35.1)	25.2%
CYVADIC	10.4 (8.4–41.9)	23.3%

p = 0.84), median progression-free survival (PFS) (17 *vs.* 16.1 month, p = 0.83), and overall survival (48 *vs.* 51 months, p = 0.483) between the group of patients with MPNST (n = 175) and other types of STS (n = 2,500) when assessed for patients with unresectable sarcomas or metastatic patients treated with chemotherapy. The chemotherapy regimen was an independent prognostic factor for response to treatment and progression-free survival, but it did not affect overall survival, which was mainly dependent on performance status [75]. Chemotherapy regimens are grouped into four main categories: anthracycline monotherapy (doxorubicin 75 mg/m^2, pegylated liposomal doxorubicin, epirubicin 75 mg/m^2, 3 × 50 mg/m^2, 150 mg/m^2), ifosfamide monotherapy (5 mg/m^2, 3 × 3 mg/m^2, 9 mg/m^2, 12 mg/m^2), doxorubicin combined with ifosfamide (50 mg/m^2 + 5 mg/m^2, 75 mg/m^2 + 5 mg/m^2), and cyclophosphamide, vincristine, Adriamycin, and dacarbazine (CYVADIC) (Table 1).

Patients who received the doxorubicin and ifosfamide regimen achieved a longer PFS compared to patients treated with anthracycline monotherapy (HR 0.807, 95% CI 0.48–1.358), and those treated with ifosfamide monotherapy had the shortest PFS (HR 2.018, 95% CI 1.155–3.327). Furthermore, the AI scheme was associated with the highest percentage of objective response rates (HR 6.283, 95% CI 2.342–16.852), and IFO with the worst ones (HR 0.33, 95% CI 0.038–2.912) [75]. In addition, based on a retrospective analysis, it was found that the combinations of doxorubicin and ifosfamide have the lowest risk of recurrence and the best response rate in patients with MPNST, despite the fact that EORTC62851 did not show differences in PFS, OS, and RR between patients treated with doxorubicin 75 mg/m^2 and AI combination at doses of 50 mg/m^2 + 5 mg/m^2 in the general population of patients with STS [76]. A randomised phase III study EORT62012 comparing doxorubicin 75 mg/m^2 as monotherapy and doxorubicin in combination with a higher dose of ifosfamide (10 mg/m^2) also showed no effect on OS (12.8 *vs.* 14.3 months, HR 0.83, 95% CI 0.67–1.03, p = 0.076), but patients treated with the addition of ifosfamide had significantly longer PFS (7.4 *vs.* 4.7 months, HR 0.74, 95% CI 0.6–0.9, p = 0.003) and a higher percentage of complete responses (26% *vs.* 14%, p = 0.0006). This study was conducted among 455 patients with STS, but the results of subgroup analysis in different types of sarcomas, including MPNST, are unavailable [77].

Anthracycline monotherapy is characterised by a similar PFS as for schemes combined with ifosfamide (AI), which indicates the possibility of using monotherapy, especially in patients whose main goal of treatment is metastatic disease control. If the goal of treatment is to alleviate the severe symptoms associated, for example, with infiltration and pressure on the nerves, or to obtain a potential resection of the tumour and/or metastasis, then it seems reasonable to add ifosfamide to doxorubicin. When selecting a chemotherapy in clinical practice, the toxicity of the selected regimen should also be taken into account. The combination of doxorubicin and ifosfamide is more myelotoxic as compared to doxorubicin monotherapy [76, 77]. Leukopenia, neutropenia, febrile neutropenia, anaemia, or thrombocytopaenia in stages 3 and 4 according to CTCAE were significantly more common among patients treated with doxorubicin and ifosfamide in the STS population [77].

In Italian and German paediatric populations the response rate in patients treated with ifosfamide-containing regimens was 65%, cyclophosphamide — 17%, and others (including those containing etoposide or cisplatin) — 20%. The schedules used did not contain or contained a low dose of anthracyclines, and an analysis of subgroups treated with this compound was not carried out [56].

In most retrospective analyses, doxorubicin was used alone or in combination with ifosfamide. In the French Sarcoma group, 102 patients with metastatic or unresectable disease (72%, 102/142) received a schedule containing doxorubicin, of which 38 (37%) were monotherapy and 64 (63%) in combination with isoniazid [70]. In another single-centre French study (retrospective), six courses of doxorubicin at a dose of 60 mg/m^2 were used, and patients with performance status 0–1 were treated with ifosfamide 2500 mg/m^2 for 1–3 days. Due to the small sample size (n = 21), in different clinical stage and different surgical status (and degree of resection), the effectiveness of chemotherapy between the schemas was not compared [78].

Targeted treatment and clinical trials

Although preclinical studies have shown the expression of proteins that are targets of known targeted drugs such as PDGFRA, PDGFRB, MET, IGFR, and AXL [79], there is currently no standard targeted therapy for patients with MPNST. Pre-clinical studies also pointed to the important role of EGFR in the development of MPNST, but further studies showed that only in 3.1% of MPNST EGFR undergoes phosphorylation and activation [80]. Molecular data are also confirmed by the results of the phase II study, which showed a lack of efficacy of the EGFR inhibitor — erlotinib — in patients with unresectable or metastatic MPNST (18/20 PD) [81]. The lack of MPNST treatment efficacy was also noted in phase II studies with sorafenib (PFS 1.7 months), imatinib (without PR or SD), dasatinib (SRC kinases inhibitor — Sprycel; no PR or SD after four courses), and alisertib (Aurora A kinase inhibitor — MLN8237; 60% PSF after 12 weeks), a combination of bevacizumab with everolimus (without PR, SD in three patients — SARC016 study), or a combination of ganetespib with sirolimus (inhibitor HSP 90 and mTORi; no PR, one SD after four cycles — SARC023 study) [41, 82–85].

Based on the results of a clinical trial PALETTE pazopanib (800 mg daily) — a multi-kinase inhibitor of tyrosine kinases — is recommended as the gold standard for the treatment of metastatic non-adipocytic STS patients after failure of standard chemotherapy. In a small series of patients treated in a Korean centre, one of five MPNST patients had a partial response and four had disease stabilisation. The median PFS was 6.5 months (0.7–12.3) and OS 8.9 months (3.5–14.3). PFS was significantly longer than in patients diagnosed with liposarcoma or RMS, and was comparable to PFS in patients with leiomyosarcoma, MFH/UPS and synovial sarcoma [86]. In a retrospective analysis of 156 STS patients treated in Japan, none of the seven patients with MPNST achieved PR, three achieved SD, 0 — SD > 6 months. Response and PFS rates in MPNST patients were significantly worse than in the general population and other histological types (PFS MPNST *vs.* non-MPNST: HR, 2.24, 95% CI 1.035–4.849, p = 0.03) [87]. The median PFS was 7.4 weeks, and the median OS was 2.5 months [87].

There are phase 1/2 or 2 clinical trials currently underway (recruiting) using the following drugs in the treatment of MPNST in unresectable patients/M1:
- pembrolizumab — NCT02691026;
- nivolumab in combination with ipilimumab — NCT02834013;
- pexidartinib (KIT, CSF1R, and FLT3 inhibitor) in combination with sirolimus — NCT02584647 [88];
- sapanisertib (TORC1/2 INK128 inhibitor) compared to pazopanib — NCT02601209;
- LOXO-195 (inhibitor of neurotrophic tyrosine kinase [NTRK] receptors type 1 [NTRK1], 2 [NTRK2], and 3 [NTRK3]) — NCT03215511;
- CPI-0610 (BET protein inhibitor) — NCT02986919;
- doxorubicin (+ dexrazoxane) in combination with olaratumab (anti-PDGFR alpha) — NCT02584309;
- doxorubicin in combination with ribociclib (D1/CDK4 and D3/CDK6 inhibitor) — NCT03009201;
- pazopanib in combination with gemcitabine — NCT01532687;
- autologous tumour lysate-loaded dendritic cell vaccine — NCT01883518.

Survival and prognostic factors

Most of the data on prognostic and predictive factors in MPNST come from retrospective single-centre analyses covering from several dozen to 200 patients. Due to the relatively low incidence of this type of cancer, discrepancies in factors affecting survival are quite large between different authors. Greater five-year survival was noted in patients after complete removal of the lesion, with a tumour diagnosed below 5 cm, and a low clinical stage. This means that the classic clinical and pathological prognostic factors in the case of MPNST include:
- location (prognosis is more beneficial with tumours located within limbs);
- tumour size (up to 5 cm);
- type I neurofibromatosis (aggravates the prognosis);
- mitotic index;
- pathological grade G;
- degree of necrosis;
- previous irradiation in the course of another disease (possibility of inducing MPNST).

Tumour size is one of the most frequently reported factors associated with negative prognosis [68, 69, 74, 89]. Discrepancies relate to the cut-off point, but it is generally accepted that tumours with a diameter above 5 cm are associated with a shorter survival; however, in some analyses an even worse prognosis for tumours > 15 cm was noted [72]. The large size of the tumour is also associated with a shorter time to chemotherapy failure [78]. Another important factor is the grade of tumour histological malignancy (grade, feature G). High-grade MPNSTs are characterised by a significantly shorter disease-free survival and overall survival [39, 69–71], which is related among others to significantly higher risk of distant metastases development [39, 74]. Grade III malignancy tumours are associated with 1.5 times shorter disease-free survival and even 3.5 times worse overall survival than grade I and II tumours [70].

In addition to the size, the location of tumours is also an important factor. Deep location of the tumour, e.g. in

the retroperitoneal space, is a negative prognostic factor for DFS and OS [70]. Patients with axial localisation of tumours have shorter DFS and OS than patients with tumours localised on limbs [72]. The presence of distant metastases is a negative prognostic factor [69]. Also, local disease advancement (e.g. infiltration of adjacent structures) is associated with worse DFS and OS [70].

Numerous controversies are related to the influence of the *NF1* mutation on the survival of patients with MPNST. Some analyses show significantly worse treatment responses and shorter survival in *NF1*-related MPNST patients, compared to sporadic ones, where five-year overall survival is shorter by up to 50% [39, 56, 90]. Taking into account only the studies published after 2000, Kolberg et al. proved that the *NF1* mutation does not significantly affect differences in survival [69]. These discrepancies may be due to the development of better strategies for monitoring patients with NF1 and the earlier implementation of treatment in those with abnormalities in imaging tests or alarm symptoms. It is also worth noting that the presence of MPNST in the family is a risk factor for the disease in patients with NF1, as well as its early development [91]. Female gender is less often a negative prognostic factor [39].

Summary and conclusions

MPNST is a malignant neoplasm of peripheral nerves, usually arising in connection with nerve trunks of the limbs and torso. It can develop *de novo* or on the basis of an already existing neurofibroma. The main risk factor for this cancer is type 1 neurofibromatosis (von Recklinghausen disease). The diagnosis is determined by histopathological examination of the sample obtained by open biopsy. As in the case of other soft tissue sarcomas, excision of a tumour with a diameter of less than 5 cm is not an error (excisional biopsy). These principles are also used in patients with type 1 neurofibromatosis, in whom large, centrally located neurofibromas require close monitoring, and excision or biopsy in suspected cases. An important clinical issue remains the differentiation between benign lesions (neurofibromas) and sarcoma lesions in patients diagnosed with NF1, with a large number of nodules. PET-CT can be helpful in differentiating these states. The radical surgical treatment — tumour excision, within the margins of healthy tissues (wide local excision), combined with complementary radiotherapy in case of R1/2 resection — is of primary importance in the treatment of neurosarcomas. Selected patients have neoadjuvant chemotherapy followed by surgical treatment. In cases of locally advanced or generalised disease, palliative chemotherapy is used, with a combination of doxorubicin or doxorubicin with ifosfamide. Clinical improvement after chemotherapy is observed in approximately 25–30% of patients [6, 55, 92]. To develop predictive biomarkers and effective strategies for the prevention and treatment of MPNST, further work is needed to identify genetic changes that contribute to cell transformation to MPNST, and progression and metastasis of MPNST. It is necessary to plan longitudinal studies with observation of patients, biobanking, and analysis of clinical and radiological data [41]. In conclusion, although the results on the treatment of MPNST have not changed significantly so far, in recent years remarkable progress has been made in understanding the biology and pathogenesis of these tumours. These advances are translated into preclinical and clinical studies with targeted therapies and give hope for the identification of active therapies for MPNST and their biomarkers. New studies that will assess the effectiveness of new treatments, including immunotherapy and a combination of chemotherapy or targeted treatment and immunotherapy, seem justified [92].

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