

## Adjuvant Treatment For Patients With Malignant Peripheral Nerve Sheath Tumours

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### Introduction

In current clinical practice, there are no curative treatment options for the aggressive neuroectodermal cancer malignant peripheral nerve sheath tumor (MPNST) beyond surgical resection [1]. Nearly one half of the patients have neurofibromatosis type 1 (NF1), a cancer predisposition syndrome that increases the risk of MPNST almost 5000 times as compared to the general population, and MPNST patients with NF1 have been reported to have worse prognosis [2], although the differences in outcome seem to have diminished in recent years. For both NF1 and non-NF1 patients, the 5-year overall survival after MPNST diagnosis is between 30 and 50% [1]. MPNSTs account for about 5-10% of soft tissue cancers treated in sarcoma units [3], including pediatric units [4], and general soft-tissue sarcoma treatment protocols, mainly including doxorubicin and ifosfamide, but also cyclophosphamide and vincristine, are often applied without any consistently documented benefit for the MPNST patients [4,5]. The effect of radiotherapy is also limited. In order to improve the poor prospects for these patients, there is clearly a need for a new approach.

There are on-going clinical trials for patients with metastatic or refractory disease including novel targeted treatments, such as the HSP90 inhibitor ganetespib [6], or the VEGF inhibitor bevacizumab in combination with the mTOR inhibitors sirolimus or everolimus, respectively. However, no molecular markers have so far been implemented in the clinic for selection of patients that could be particularly susceptible to any of these treatments, and several previous trials using targeted drugs, such as erlotinib [7], sorafenib [8], imatinib [9], and dasatinib [10] reported hardly any response against MPNST. Recent advances in DNA sequencing technology have revealed novel putative targets in MPNSTs that have so far not been tested in a clinical setting, such as the mutations in components of the polycomb repressor complex 2, SUZ12 and EED [11-13]. In combination with the discovery of novel targets, there is also a need for better tools for selecting high risk patients among those in complete remission after the initial surgery, as almost half of them will experience disease progression within the first few years.

### Risk stratification and hints towards new treatment options

In a recent paper, we described an immuno histochemical profile with the potential to stratify patients into high and low risk groups, also for patients in complete remission after surgery [14]. The profile is based on nuclear expression of three proteins in tissue sections of MPNST: TOP2A, TK1, and BIRC5, each encoded on chromosome arm

17q which is frequently amplified in MPNST [15-17]. We found that each of these three proteins had independent prognostic value, not only on the protein level, but also on the gene expression level and the DNA copy number level [14]. In addition, the three proteins are themselves potential drug targets, or involved in drug metabolism that hints towards possible new treatment strategies. Thus, these biomarkers may function not only as prognostic but also as predictive factors guiding therapy.

In a recent phase II clinical trial against stage III and IV (metastatic) MPNST (NCT00304083, SARC006), etoposide and doxorubicin targeting TOP2A were utilized in combination with the alkylating agent ifosfamide [18]. The objective response (OR; i.e., complete response (CR)+partial response (PR)) goal at 40% for the trial was not met. Interestingly, however, out of 41 patients presented, PR was observed for 9 patients and stable disease (SD) for 27. There was a slightly better response for the sporadic MPNSTs (OR=33%) as compared to the neurofibromatosis type 1 (NF1) associated MPNSTs (OR=17%), although this difference was not significant (two sided Fisher exact test P=0.41). We speculate that a preselection of patients using our IHC profile might have improved these results, and possibly pushed the OR above the 40% limit. Specifically, stage II patients with a high risk IHC profile could have been included in the study, as these are likely to develop relapse. Furthermore, although there is still little data to supporting protein expression of TOP2A as a predictive marker for anti-TOP2A treatment, our data suggest that most patients with low TOP2A are at low risk of developing relapse, and that these patients therefore possibly could have been excluded from the trial using etoposide and doxorubicin.

The second prognostic marker, thymidine kinase 1 (TK1), is itself a drug target; the viral ortholog is established in antiviral therapy, and explorative clinical trials in suicide gene therapy against cancer have been investigated [19]. TK1 is also a putative serum biomarker for monitoring disease [20]. In addition, TK1 is part of the so-called 5-FU pathway, which is necessary for generating the active form of the well-established drug 5-fluorouracil (5-FU) and related compounds, such as floxuridine. 5-FU is a well-known chemotherapeutic agent and utilized in many cancer types, but to our knowledge, there has never been any systematic trial for 5-FU in MPNST, nor any case report. From our gene expression data, we have evidence that other enzymes involved in thymidine metabolism, in addition to TK1, are selectively enriched in MPNST, including TYMS and RRM2, which further supports the 5-FU drugs as relevant candidate drugs in MPNST.

The final component of the IHC profile, BIRC5 (aka survivin, an antiapoptotic protein), has been suggested as a drug target for MPNST [21,22], and several trials using survivin inhibitors (e.g. YM155, FL118 and 5-deazaflavine) have been performed for different cancer types over the past few years [23]. Novel gene silencing strategies using siRNAs or LNA-siRNAs have also been reported, as well as immunotherapy using dendritic cells expressing survivin as a tumor antigen [24,25]. So far, however, none of these strategies have received final approval for clinical use.

## Conclusions

MPNST is a rare cancer with an incidence of less than 1 in 1 000 000 [26]. The low number of patients also limits the statistical power of the few clinical trials that have been initiated. The general clinical experience with MPNST is that these patients respond poorly to adjuvant treatment, and there is a great need for new treatment options for this patient group. We have recently described an IHC profile in MPNST identifying prognostic factors that are also targets to the well-known cytostatic drugs, etoposide and 5-FU rarely used in the treatment of MPNST. To further explore these findings, we suggest a clinical trial guiding therapy in MPNST based on the expression of these biomarkers.

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