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Tumour Review

Recent developments and current concepts in medulloblastoma

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ABSTRACT

Medulloblastoma is the most common malignant brain tumor of childhood. While prognosis has significantly improved in the last decades with multimodal therapy including surgery, radiotherapy, and chemotherapy, one third of patients still succumb to their disease. Further research is needed to find more efficient treatment strategies for prognostically unfavorable patient groups and to minimize long-term sequelae of tumor treatment. This review gives a summary of the current state of treatment concepts including an outlook on the near future. We describe recent advances in the understanding of molecular mechanisms, their potential impact on risk stratification in upcoming clinical trials, and perspectives for the clinical implementation of targeted therapies.

Introduction

Medulloblastoma (MB), an embryonal tumor of the cerebellum, is the most common malignant brain tumor of childhood. It occurs at all ages, peaking in incidence between 4 and 7 years, while rarely diagnosed in adults [1–3]. It has the propensity to disseminate along the cerebrospinal fluid (CSF) pathway, and metastatic disease at diagnosis is found in approximately 30% of patients. Spread outside the central nervous system (CNS) is very rare at diagnosis. While some genetic disorders (i.e. Gorlin syndrome, Turcot syndrome, Li-Fraumeni syndrome, Rubinstein-Taybi syndrome, and ataxia telangiectasia) are associated with an increased risk of MB, for most patients the etiology is unknown [2,4]. The management of MB has evolved over the last 3 decades as a result of prospective multicentric clinical trials. Multimodal treatment including surgical resection, radiotherapy, and chemotherapy has led to an improvement of outcomes with around two thirds of the patients being long-term survivors [5]. However, treatment-related toxicity often has a major impact on long-term quality of survival. In order to reduce sequelae, the concept of stratification into risk groups according to clinical variables (e.g. age, presence of metastases detected by imaging or cytological evaluation of CSF, and post-operative residual tumor status) has been developed in the last decades, adjusting the intensity of therapy to the risk of relapse [6]. While the principal treatment strategies have not significantly changed over the past few years, enormous progress has been made in understanding of tumor biology, which has led and most likely will continue to lead to further refinements of risk stratification and to the development of novel therapy approaches using targeted drugs in a personalized way [7].

In this review, we present a summary of clinical characteristics, diagnostic measures, surgical aspects, and the currently used risk stratification, followed by a view on molecular biologic advances and their implications on future stratification and therapy in upcoming clinical trials. We then describe current and future treatment strategies for different patient subgroups, followed by a section on late sequelae, focusing on neurotoxicity.

Clinical diagnosis, staging, and surgical treatment

The median interval from the first symptoms to the diagnosis is two months with a range from days to possibly years [8]. Presenting symptoms and signs usually arise from hydrocephalus or cerebellar dysfunction, and comprise vomiting, macrocephalus, loss of developmental achievements in infants, and headache, vomiting, ataxia, and cranial nerve palsy in older patients. Magnetic resonance imaging (MRI) shows a cerebellar tumor, often with compression of the fourth ventricle and dilatation of the lateral and the third ventricles due to obstruction of the CSF flow. Besides

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the cranial MRI, the assessment for metastases comprises a spinal MRI and a cytological assessment of the lumbar CSF.

Although a short prediagnostic symptomatic interval has not been associated with a better survival in medulloblastoma [8], this does not justify delays in diagnostic procedures. In the individual patient, delayed diagnosis may lead to potentially life-threatening complications of intracranial hypertension and may have adverse effects on neurological and neuro-psychological outcome as well as quality of life.

The aims of surgery are a maximum resection of the primary tumor with minimal damage of neurological function in order to reduce any mass effect, to debulk vital tumor tissue, to establish the biopathological diagnosis, and, if possible, to restore CSF flow. In view of the efficacy of the adjuvant treatment, a microsurgically complete resection should only be intended in case of tolerable risk. Complications of tumor surgery include bleeding, transient diabetes insipidus, syndrome of inappropriate antidiuretic hormone secretion, infection, and non-obstructive hydrocephalus. Among the neurological complications, posterior fossa syndrome is of special relevance affecting one quarter of patients and consisting of mutism, swallowing difficulties, truncal ataxia, and emotional instability. Symptoms typically appear within 24–48 h after surgery, may persist for months longer and often are associated with long-term neurocognitive impairment [9–11]. While the pathogenesis is not fully understood, injury of the dentate-thalamic-cortical tracts has been implicated, and surgical measures such as a telovelar approach avoiding the splitting of the vermis have been advocated to reduce the risk [12]. Clinically, left-handedness, MB histology and localized damage within the right cerebello-thalamo-cortical pathway have been identified as risk factors for posterior fossa syndrome in a series of children with posterior fossa tumors [13].

A high percentage of patients present with obstructive hydrocephalus at diagnosis. There is no consensus on the optimum management. While in a part of the patients the CSF flow can be restored by the tumor resection itself (in some patients following the placement of an external ventricular diversion due to a transient tumor- or surgery-induced disturbance of CSF flow), a ventriculoperitoneal shunt is implanted in a significant portion of patients. Pre-resectional endoscopic third ventriculostomy has been suggested as an efficient alternative measure [14].

In order to minimize the risk of artifacts, the post-operative MRI, which is performed to assess the residual tumor status, should be performed in the first 72 h after surgery. Some groups prefer to have the MRI between 24 and 72 h after surgery. The value of intraoperative MRI is not clear yet. In case of significant residual tumor, particularly in non-metastatic disease, second-look surgery should be discussed either directly after the primary operation or in the course of further treatment. For staging, the clinical classification according to the modified Chang system [15] has been generally accepted. It comprises an MRI examination of the full craniospinal axis and an evaluation of lumbar CSF cytology. As immediate post-operative assessment of CSF can yield false positive results due to surgical detritus, the optimum timeframe for lumbar puncture is between 14 days after surgery and start of adjuvant treatment. Postoperative contrast enhancement (sometimes up to a few weeks) and post-punctional MRI alterations (e.g. subdural enhancement) may be difficult to distinguish from metastases or laminar meningeosis. Therefore, spinal MRI should be performed before lumbar puncture or – in case of suspicion of MB – ideally even before tumor surgery.

Current risk stratification

Starting in the mid-twentieth century, the first decades of curative MB treatment were characterized by a growing number of long-term survivors by means of gradual treatment intensification, albeit often at the price of a relevant impairment of quality of life [16]. In the past two decades, with increasing knowledge on clinical risk factors, stratification of patients into different risk groups has allowed controlled de-escalation of treatment intensity within clinical trials. Established risk factors for an adverse prognosis in terms of progression-free and overall survival are: metastatic disease at diagnosis, a residual tumor of >1.5 cm [2] (largest extent in an axial plane) on post-operative imaging, young age, and anaplastic or large-cell histological subtype (for summary see Table 1). For past and currently open trials, MB in patients aged from 3 to 5 years up to 21 years at diagnosis with gross-total or near total resection, without macroscopic or CSF metastases, and, in most trials, with non-anaplastic and non-large-cell histological subtype has been considered as 'standard-risk' (or 'average-risk') disease, while the other patients are counted as 'high-risk', with infants and very young children posing particular therapeutic challenges [6,17–23].

Tumor biology – new insights and their possible impact on future risk stratification and targeted therapy

Despite the merits of a risk stratification based on clinical factors, the outcome of patients within the distinct risk groups is still highly heterogeneous. Thus, a purely clinical stratification algorithm has not proved satisfactory. The increasing knowledge of biologic heterogeneity of MB has led to a paradigm shift holding the promise of a much better tailored approach to risk stratification. The first approach towards 'biologic' MB subgrouping was based on histology, dividing these tumors into classic, large-cell, anaplastic, desmoplastic variants, and MB with extensively nodularity [2,24]. Together with clinical factors, histological subtyping has been increasingly used for prognostication and stratification. For example, patients with large-cell morphology or anaplasia were excluded from the standard-risk group in several trials due to their adverse prognosis in other series [22], while in infants and young children desmoplasia and extensive nodularity were shown to be prognostically favorable [23]. As for molecular biologic factors, in the last decade the focus lay on the exploration of one or two handful of markers [25]. Among others, the nuclear accumulation of beta-catenin [26], and the mRNA expression level of the neurotrophin receptor TrkC [27] were found to be associated with a favorable outcome, while the opposite was shown in tumors with myc amplification [22,28], and chromosome 17 imbalance [29] (Table 1).

In the past few years, knowledge about MB biology has evolved faster than ever by the use of high-throughput methods for transcriptomics. Based on gene expression patterns in tumor tissue, MB can be classified into distinct subgroups [30–33]. According to the current consensus, four main groups can be distinguished: WNT, SHH, Group 3, and Group 4 (Fig. 1) [34,35]. Most likely, biological classification will continue to evolve, and further refined subgrouping has already been suggested [7,35,36], Table 2 gives an outlook on a possible future risk classification in medulloblastoma.

WNT group medulloblastoma

In this group, comprising roughly 10% of MBs, somatic mutations in the CTNNB1 gene encoding β-catenin (often associated with monosomy 6) leads to a hyperactivation of the WNT pathway by rendering β-catenin resistant to degradation, leading to nuclear accumulation of the protein and consecutive transcription of genes involved in proliferation. A minority of patients have a germline mutation in the APC tumor suppressor gene, which results in loss of inhibition of the WNT pathway in individuals with Turcot