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A long duration of the prediagnostic symptomatic interval is not associated with an unfavourable prognosis in childhood medulloblastoma

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ABSTRACT

Background: Due to the lacking specificity of symptoms making a correct diagnosis can be a challenge in children with medulloblastoma. This can lead to prediagnostic symptomatic intervals (PSIs) of several weeks to months. It is unknown whether the length of the PSI is associated with an inferior survival outcome in this population.

Methods: To study the association of PSI with disease stage at diagnosis, tumour control and survival in children with medulloblastoma, prospectively collected data on PSI, clinical, and biological features were analysed in 224 patients diagnosed at the age of 3–18 years and treated within the prospective randomised multicentre trial HIT'91.

Results: Patients with lower-stage disease tended towards a longer median PSI than those with higher-stage disease (M0 stage, 2.0 months; M1 stage, 2.0 months; M2/M3 stage, 1 month; $p = 0.094$. M0/1 stage versus M2/3 stage; $p = 0.025$). The patient group with the longest PSI had the best survival outcome (PSI $\geqslant$4.0 months: 10-year overall survival rate (OS), 71%; PSI <4.0 months, 10-year OS, 61%; $p = 0.056$). Age at diagnosis was positively correlated with PSI ($p = 0.027$). No associations were found between PSI and sex histological subtype, presence of postoperative residual tumour, or c-myc and TrkC mRNA expression.

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Conclusion: Contrary to a common belief that a longer PSI may adversely affect prognosis, a longer PSI was associated with a trend towards lower metastatic stage and better survival probabilities. Nevertheless these findings do not obviate the importance of a timely diagnosis in paediatric patients with medulloblastoma.

1. Introduction

Medulloblastoma is a primitive neuroectodermal tumour of the cerebellum with a tendency to metastasise by leptomeningeal spread. It is the most common malignant brain tumour in paediatric patients accounting for 20% of all central nervous system tumours. Advances in diagnostic, surgical, radiotherapeutic and chemotherapeutic methods have led to markedly improved survival outcome in the last decades. However, a significant proportion of patients still succumb to their disease.[1,2]

Making a correct diagnosis can be a challenge due to often non-specific symptoms and signs which not only depend on the tumour itself, but also on the patient's age and developmental stage.[3] This can lead to prediagnostic symptomatic intervals (PSI) ('diagnostic time lags') in the range of several weeks to months.[4–11] The assumption that a longer PSI may result in a more advanced disease stage and/or have an adverse impact on tumour control, survival and/or neurological/neuropsychological/quality of survival outcome may lead to self-reproaches in parents and physicians and can result in accusations of medical malpractice.[12–14] However, there is not enough information on the correctness of this assumption, as studies on PSI in children with brain tumours suffer from low patient numbers, retrospective design, heterogeneity of patient, disease, and treatment characteristics, and lacking outcome data.[4–11,15–24]

To study the association of the PSI with disease stage at diagnosis as well as tumour control and survival outcome, we analysed prospectively collected data on 224 homogeneously treated patients.

2. Methods

2.1. Patients and diagnostic procedures

Between August 1991 and December 1997, 280 patients between 3 and 18 years of age with newly diagnosed medulloblastoma were treated according to the prospective randomised multicentre HIT'91 trial, as previously described.[2,25] Recommended staging included pre- and postoperative cranial magnetic resonance imaging (MRI) or computed tomography (CT), spinal MRI, and evaluation of cerebrospinal fluid (CSF) cytology.[26] Central review of histopathology, CSF cytology, and CT/MRI scans was recommended. mRNA expression levels of c-myc and TrkC in tumour tissue were measured as described.[27] Duration of the prediagnostic symptomatic interval (PSI), i.e. the interval between the appearance of the first symptom/sign judged as unambiguously related to the tumour disease by the treating oncologist and diagnosis, as well as the nature of the presenting symptoms and signs were prospectively recorded. A PSI value was available for 266 of 280 (95%) patients. The current analysis is restricted to those 224 of 280 (80%) patients for whom the PSI value and central histopathological review of tumour tissue were available. Complete radiology/cerebrospinal fluid staging for metastases was performed in 184 (82%) of the 224 study patients.

2.2. Treatment

After obtaining approval of the study protocol from the appropriate ethical committees and informed consent from all patients and/or their legal representatives, patients were randomly assigned to receive either immediate postoperative radiotherapy (35.2 Gray [Gy] to the craniospinal axis followed by a boost to the posterior fossa to a total of 55.2 Gy and to any supratentorial and spinal metastases to 50.0 Gy, with concomitant vincristine) followed by 'maintenance' chemotherapy (CCNU, vincristine, and cisplatin), or immediate post-operative pre-radiation 'sandwich' chemotherapy (ifosfamide, etoposide, methotrexate, cisplatin, and cytarabine) followed by radiotherapy and, in case of non-complete response thereafter, additional 'maintenance' chemotherapy, as previously described.[2,25]

2.3. Statistical analyses

Kaplan–Meier estimates and log-rank test were used for overall survival (OS) and progression-free survival (PFS) rates (±standard errors), with OS measured from primary surgery to death of any cause or last evaluation, whichever came first, and PFS measured from primary surgery to first documented progressive disease, to death of any cause, or to last evaluation, whichever came first. To analyse the association of the duration of the PSI with survival, patients were divided into quartiles according to their PSI. For multivariable analyses, Cox regression models with forward and backward stepwise selection (inclusion criterion: p-value of the score test $\leqslant 0.05$, exclusion criterion: p-value of the likelihood ratio test $\geqslant 0.10$) were used to analyse the possible impact of the following variables: age (continuous and categorical [3–8 versus 8–13 versus 13–18]), sex (categorical), stage (categorical: M0 versus M1 versus M2/3 versus incomplete staging; M0/1 versus M2/3 versus incomplete staging; M0 versus M1/2/3 versus incomplete staging), histological subtype (categorical, classic versus desmoplastic versus large cell/anaplastic), residual tumour (categorical), therapy arm (categorical), PSI (continuous and categorical [group]), c-myc mRNA expression (categorical [$\leqslant 1$ versus >1 versus no value available]), and TrkC mRNA expression (categorical [$\leqslant 1$ versus >1 versus no value available]). For Cox regression, p-values of the likelihood ratio test