European Journal of Cancer (2012) xxx, xxx–xxx

Available at www.sciencedirect.com

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journal homepage: www.ejcancer.info

Treatment of adult nonmetastatic medulloblastoma patients according to the paediatric HIT 2000 protocol: A prospective observational multicentre study

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KEYWORDS
Brain tumour
Medulloblastoma
Adults
Treatment
Radiotherapy
Chemotherapy

Abstract ***Background:*** Medulloblastoma in adulthood is rare. Knowledge is limited, and the efficacy and toxicity of chemotherapy – especially in nonmetastatic disease – is still elusive.
Methods: Seventy adults aged ⩾21 years (median age: 28.5 years) with nonmetastatic medulloblastoma were followed as observational patients within the prospective paediatric multicentre trial HIT 2000. Treatment consisted of radiotherapy (35.2 Gy to the craniospinal axis and a boost to 55.2 Gy to the posterior fossa) followed in most patients by maintenance chemotherapy (lomustine (CCNU), vincristine and cisplatin, $n = 49$).
Results: The implementation of maintenance chemotherapy was feasible. Peripheral neuropathy (74%) and haematotoxicity (55%) during maintenance chemotherapy appear to be more common in adults than in children. At a median follow-up of 3.7 years, the 4-year event-free survival (EFS) and overall survival (OS) rates ± standard error (SE) were 68% ± 7% and 89% ± 5%. Patients with desmoplastic medulloblastoma and lateral tumour location ($n = 19$) had a lower EFS compared to patients with centrally located desmoplastic tumours ($n = 10$) ($p = 0.011$). Absence of residual postoperative tumour ($n = 40$) was associated to a

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0959-8049/$ - see front matter
http://dx.doi.org/10.1016/j.ejca.2012.10.006

Please cite this article in press as: Friedrich C. et al., Treatment of adult nonmetastatic medulloblastoma patients according to the paediatric HIT 2000 protocol: A prospective observational multicentre study, *Eur J Cancer* (2012), http://dx.doi.org/10.1016/j.ejca.2012.10.006

lower rate of progression/relapse compared to present ($n = 11$) or unknown ($n = 12$) residual tumour status ($p = 0.006$). Lateral tumour location and unknown residual tumour status were independent negative prognostic factors.

Conclusions: Maintenance chemotherapy is applicable in adults with nonmetastatic medulloblastoma. Histological subtype and tumour location were newly identified risk factors in this age-group, and should be further analysed in prospective trials.

1. Introduction

Medulloblastoma (MB) is an embryonal tumour of the cerebellum that disseminates within the central nervous system (CNS). Whereas it is the most common malignant brain tumour in children, it accounts for less than 1% of CNS tumours in adults.[1] Nevertheless, around 24% of medulloblastoma patients are diagnosed at 21–40 years of age.[2]

So far, the postoperative therapy of nonmetastatic MB in adults frequently consists of craniospinal irradiation (CSI) only. Rates for 5-year progression-free survival (PFS) for adults with nonmetastatic MB have been reported between 40% and 80%.[3] However, only a few mainly retrospective monocentric/oligocentric studies analysed the impact of chemotherapy on survival and toxicity, and the use of different treatment regimens within those studies makes it difficult to draw conclusions.[2,4–9] In a prospective trial, adults with average-risk MB ($n = 10$) were treated without chemotherapy by adjuvant CSI only resulting in a 5-year PFS rate of 80% and a 5-year overall survival (OS) rate of 80%.[3,10] The prospective multicentre trial HIT'91 of the German Society of Pediatric Oncology and Hematology (GPOH) for MB patients aged 3–18 years demonstrated a favourable long-term outcome for nonmetastatic disease treated with postoperative CSI followed by maintenance chemotherapy consisting of cisplatin, lomustine (CCNU) and vincristine (10-year event-free survival (EFS) rate ± standard error (SE): 83% ± 6%; 10-year OS rate ± SE: 91% ± 4%).[11,12] Here, we report on a large observational study of adults with nonmetastatic MB that were treated within the prospective multicentre trial HIT 2000 by postoperative CSI and maintenance chemotherapy in most cases. We aimed to prospectively evaluate treatment toxicities, modifications and whether the encouraging results of the HIT'91 study can be reproduced in adults.

2. Patients and methods

2.1. Patient characteristics

Patients aged ⩾21 years were not meeting the inclusion criteria for the HIT 2000 trial for children and adolescents conducted by the GPOH (ClinicalTrials.gov/NCT00303810) and were prospectively documented as observational patients. Similar to a registry, we provided uniform recommendations for the diagnostic evaluations and the therapy of nonmetastatic MB patients, but adherence was not mandatory for registration. Inclusion criteria for the adult nonmetastatic MB observational arm of the HIT 2000 study were diagnosis of a primary intracranial tumour, histologically confirmed diagnosis of MB by an experienced neuropathologist (T.P.) on central review or by the local institutional pathologist/neuropathologist. Patients were to have no evidence of disseminated disease. In total, 75 nonmetastatic MB patients were reported by 46 different centres in Germany. We excluded one patient (ineligible pathology: ependymoma).

Selection criteria for this analysis were no MB classified as secondary malignancy, no medical contraindication to receive protocol therapy, not having received any radio- or chemotherapy before diagnosis, no evidence for having received a different chemotherapy than the maintenance chemotherapy after craniospinal radiotherapy as primary treatment and information that a patient has survived the first day of postoperative craniospinal radiotherapy. Of the 74 observational MB patients we excluded further 4 patients from the analysis: only the date of surgery was known without further follow-up ($n = 3$), and a different maintenance therapy has been applied ($n = 1$). All institutions participating in the HIT 2000 trial had received approval from their institutional review boards, and informed consent was obtained from all patients.

2.2. Diagnostic evaluations

Patients and disease characteristics are displayed in Table 1. Central histopathological review was recommended and performed by an experienced neuropathologist (T.P.) according to the World Health Organisation classification of brain tumours.[13,14] Staging included pre- and postoperative cranial magnetic resonance imaging (MRI), spinal MRI and evaluation of cerebrospinal fluid (CSF) to exclude CSF spread. Central review was offered for imaging and CSF analysis. If tumour cells were present in the CSF, it was recommended to repeat the analysis ⩾14 days after surgery.

Complete diagnostic evaluations, as recommended, were not performed for all patients. In 50 of 70 patients (71%) complete staging assessments were verifiable. In 8

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