European Journal of Cancer 81 (2017) 1–8

Available online at www.sciencedirect.com

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journal homepage: www.ejcancer.com

Original Research

Haematological malignancies following temozolomide treatment for paediatric high-grade glioma

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Received 19 October 2016; received in revised form 25 April 2017; accepted 28 April 2017
Available online 3 June 2017

KEYWORDS
Children;
Glioblastoma;
High-grade glioma;
Secondary

Abstract ***Background:*** Temozolomide (TMZ) is widely used in high-grade glioma (HGG). There is a major concern of treatment-induced secondary haematological malignancies (SHMs). Due to the poor overall survival of HGG patients, the true incidence is yet elusive. Thus, the aim of this study was to determine the risk of SHMs following TMZ in paediatric HGG.

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http://dx.doi.org/10.1016/j.ejca.2017.04.023

haematological malignancies

Methods: We analysed 487 patients from the HIT-HGG database of the German-speaking Society of Pediatric Oncology and Hematology with follow up beyond 1 year.
Results: The incidence of SHM was 7.7 ± 3.2% at 10 years. No SHM occurred in 194 patients after first-line TMZ therapy, but four out of 131 patients treated with TMZ for relapse following first-line multiagent chemotherapy experienced SHM (20% at 10 years; $p = 0.041$). SHMs occurred in two out of 162 patients who underwent multiagent chemotherapy without TMZ (4.1% at 10 years). Gender, patient age and acute haematological toxicity during treatment did not affect the incidence of SHMs.
Conclusion: Data of our cohort do not indicate an increased risk of SHM following TMZ treatment when compared to previous chemotherapy regimen. However, if TMZ is administered as a second-line treatment following conventional chemotherapy regimen, the risk might be disproportionately increasing.

1. Introduction

Temozolomide (TMZ) has widely changed the treatment of high-grade glioma (HGG) in adults and in the paediatric population. Following tumour resection, current paediatric protocols usually recommend TMZ concomitantly to radiotherapy, followed by adjuvant TMZ [1]. The possibility of a largely outpatient treatment due to the oral application and a favourable toxicity profile has contributed to an improved quality of life for these patients whose prognosis remains poor [2,3].

However, similar to other alkylating agents, TMZ induces single- and/or double-strand DNA breaks and may therefore lead to secondary neoplasms [3]. Most reports of both children and adult patients associate TMZ with secondary haematological malignancies (SHMs). Adults predominantly experience treatment-related acute lymphoblastic leukaemia, acute myeloid leukaemia, and myelodysplasia [4–12]. This may be explained by a particularly low intrinsic O^6-methylguanine-DNA methyltransferase activity in haematopoetic cells and lymphoid tissue [13]. Due to the poor survival of HGG and the relatively recent introduction of TMZ into treatment compared with conventional chemotherapy agents, the true incidence of SHM following TMZ is yet to be clarified. However, a disproportionately increased risk of SHMs in adults seems to be associated with TMZ as a second-line treatment following preceding mutagenic agents including nimustine (ACNU) or etoposide [14].

To date, no larger series have been published with regards to incidence and risk factors of SHM following TMZ for paediatric HGG. We present the HIT-HGG experience on these fatal events. We analysed the risk of SHM following TMZ treatment in comparison to conventional multiagent chemotherapy regimens. Since treatment-induced SHM are unlikely to occur within the first year of treatment [3], survival and follow up for all 487 paediatric patients in the present study exceeded 1 year.

2. Patients and methods

2.1. Patients' characteristics and inclusion/exclusion criteria

Patient data were obtained from the HIT-HGG database of the Society of Pediatric Oncology and Hematology (Gesellschaft für Pädiatrische Onkologie und Hämatologie, GPOH) in Germany, Austria and Switzerland. This registry contains prospective clinical data of all patients enrolled in the subsequent HGG trials (HIT-GBM A-D) [15–18] as well as the ongoing HIT-HGG 2007 trial (Eudra-CT 2007-010128-42, ISRCTN19852453). In addition, the registry includes patients aged <3 years at diagnosis treated according to the HIT-SKK regimen [19]. All patients and/or their legal guardians had given informed consent for data storage and statistical analyses in accordance to national law and the Declaration of Helsinki at the time of enrolment in the various trials.

The following inclusion criteria were defined for the present study (Fig. 1):

(A) Enrolment into the clinical trials HIT-GBM-A, -B, -C, -D and HIT-HGG 2007. Very young children <3 years of age treated according to the HIT-SKK regimen were also included.
(B) Histopathological diagnosis of a HGG as defined by the third revision of the WHO classification of central nervous system tumours [20]. Patients without histopathological diagnosis were only included in case of an unequivocal centrally reviewed neuroradiological diagnosis of (a) a diffuse intrinsic pontine glioma defined by tumour infiltration of the pons by more than 50% of the total diameter in a patient with 'classical' brainstem symptoms (e.g. long tract signs, ataxia or cranial nerve deficit or a combination of any) or (b) a centrally