Meeting report on the paediatric high-grade glioma medicines expert workshop

Development of high-quality medicines to treat children with high-grade glioma

The European Medicines Agency (EMA) held an expert meeting on 3 December 2010, on questions on the development of anti-cancer medicinal products to treat children with high-grade glioma (HGG). Due to adverse weather conditions affecting the travel of many participants, it was conducted as a teleconference-based meeting.

Purpose and objectives of the expert meeting

The purpose of the workshop was to help inform the EMA and its Paediatric Committee (PDCO) on how to best compose opinions that set out detailed requirements for non-clinical and clinical paediatric studies, to provide for high-quality Paediatric investigation plans (PIPs) for this group of tumours. The objectives were to learn from invited experts about recent scientific translational developments, to hear about their experience from clinical trials in patients with HGG and to listen to their views on how non-clinical and clinical studies in children with HGG should be conducted. Information on demographics, histopathology, biology and treatments as well as on the relationship between paediatric and adult subsets and between different paediatric subsets was considered, thereby helping to define which data need to be evaluated in order to establish the safe and efficacious use of new medicinal products for HGG in the paediatric population. No confidential information was presented or discussed.

Invited experts included paediatric and adult neuro-oncologists, paediatric oncologists (from Europe and the United States), a neurosurgeon, a neuro-radiologist, a radiation therapy oncologist, translational researchers and a paediatric pharmacologist. Further participants were members of the EMA’s Paediatric Committee (PDCO), the Scientific Advice Working Party (SAWP), the Committee for Orphan Medicinal Products (COMP), the Oncology Working party (OWP) as well as scientific staff members of the EMA and the United States Food and Drug Administration (FDA).

As part of the preparation for the meeting, a questionnaire had been sent out in advance to the invited experts. This explored current views, experience and practice relating to the treatment of children with...
HGG and on clinical research involving such patients. The experts from the brain tumour group of the European branch of the International Society of Paediatric Oncology (SIOPE) had extended the questionnaire to a survey among physicians treating children with HGG, in order to reflect a broader range of experience during discussions at the expert meeting. Additional preparatory documents for the experts included a collection of abstracts and a literature list.

**Introduction to high-grade glioma in children**

HGG is a malignant tumour of the central nervous system (CNS), newly affecting (incidence) about 350 to 400 children in Europe yearly (expert view), compared to about 10000 adults in Europe (based on an annual incidence estimate of 2 in 100000). A number of prognostic factors are known, and they are differently distributed in adults and in children (see below).

After a new diagnosis of HGG, the median duration of survival (ie half of the patients live longer, half die before) is around 18-24 months in children (Qaddoumi et al. 2009; Wolff et al. 2008; Wolff et al. 2009) and around 15 months in adults (Stupp et al. 2009); the median time from diagnosis to progression is unpublished in children and around 7 months in adults (Stupp et al. 2005). Additionally, from the time of first progression or recurrence of HGG, the median time to further progression is around 7 to 10 months in adults (Lamborn et al. 2008).

Currently, outcomes in paediatric patients with HGG are generally very unfavourable. Established management in children includes maximum safe resection (or, if not possible, biopsy), followed by radiation therapy, followed by systemic anticancer chemotherapy. Different multi-agent chemotherapy regimens have been used, but they often have burdensome toxicity and provide limited benefit. For children, only one anticancer substance (temozolomide) is currently authorised specifically for HGG (for use in relapsed or progressive disease), and although it is used in children based on adult efficacy data, its benefit in children is considered modest at best.

A diffuse intrinsic pontine glioma (DIPG) is defined by characteristic imaging appearance and well-recognised clinical symptoms. This brain tumour has a dismal prognosis with a median overall survival of 8-12 months (Hargrave et al. 2006) and exhibits a highly-malignant clinical course. Although the majority of cases are diagnosed on a clinical and radiological basis only, when biopsy or autopsy material is available this is usually consistent with high-grade glioma. Recent molecular analyses have demonstrated some differences between the underlying biology of DIPG and adult/paediatric HGG found in other CNS sites, but larger series are required to confirm these preliminary findings (Zarghooni et al. 2010; Paugh et al. 2010; Barrow et al. 2011). DIPG is newly diagnosed in about 200 children (incidence) in the U.S.1

Overall, the treatment of children with HGG reflects a significant unmet need, with almost no improvement in survival outcomes in recent years.

The EMA gave a short introduction to the European Paediatric Regulation and its requirements for paediatric medicine development for the authorisation of medicinal products in children. Paediatric investigation plans (PIPs) are evaluated by the EMA’s PDCO and mandate the development of anticancer medicines for children at a stage that development in adults has progressed to therapeutic-exploratory studies, after pharmacokinetic data from adults is available. Based on an application by a pharmaceutical company, the PDCO determines the timing and details of pharmaceutical, non-clinical and paediatric clinical studies that are necessary to provide evidence of the quality, safety and efficacy of a medicine to allow its authorisation for use in children. Such paediatric studies nevertheless require favourable ethics committee review and approval by national competent authorities.
Biological data on high-grade glioma

Two presentations were given on the molecular biology of HGG. During recent years significant progress in the understanding of the molecular characteristics of HGG has been made. Most of the presented data are now published (please see references below). The emerging deeper understanding of HGG tumour biology should be regarded as essential for the improvement of drug discovery for children with HGG and the design of relevant paediatric studies.

There has, historically, been a paucity of representative paediatric model systems for childhood HGG. Non-clinical model systems for paediatric HGG currently consist mainly of limited numbers of immortalised paediatric HGG cell lines (none available via the ATCC) and a limited number of subcutaneous xenograft models (e.g., as part of the Pediatric Preclinical Testing Program, PPTP, and others). Orthotopic xenografts and genetically engineered models are being developed but are not yet sufficiently well characterised. For diffuse intrinsic pontine gliomas (DIPG), histologically and genetically accurate models are also in development.

Emerging research has shown that there are important differences in the biology of HGG between children and adults. Unlike their adult counterparts, HGG in children less commonly arise from lower grade gliomas undergoing malignant transformation (Broniscer et al. 2007). Certain molecular features and signalling pathway activation can occur in both groups but they occur with different frequencies, e.g., abnormalities in the Retinoblastoma (RB) or Phosphatidylinositol-3-Kinase (PI3K)/Mammalian target of rapamycin (mTOR) pathways. Thus \textit{PIK3CA} and \textit{PTEN} mutations are less frequent in children with HGG, compared to adults. Mutations in \textit{IDH1} or \textit{IDH2} are exceptional in paediatric patients but occur in the majority of adult patients with HGG.

Stable genome profiles may be seen in HGG in a proportion of paediatric patients, but apparently not commonly in adult patients. The most common abnormality of HGG in paediatric patients is PDGFRA amplification or overexpression. \textit{BRAF} and \textit{CDKN2A} mutations have been reported to characterise HGG in a subset of paediatric patients, although \textit{BRAF} abnormalities are not as frequently as described in childhood low grade glioma. These and other findings indicate that HGG in children overlap the classes of HGG (proneural, proliferative, mesenchymal, classical) defined in adult patients but there are key differences in the underlying biology.

Some characteristics can be correlated with paediatric or adult age groups, anatomical location in the CNS and other biological features. However, other characteristics seem to be similarly distributed across histological subtypes and locations, and thus might be age-independent prognostic factors, such as genomic imbalances, certain \textit{HOX} gene signatures, \textit{BMP}, \textit{OBSCN}, \textit{PARP1}, \textit{CDKN1A}, \textit{NUMB}, neural differentiation etc.

DIPG may be characterised by amplifications in \textit{PDGFRA}, \textit{MET}, \textit{IGF1R} and genetic losses in \textit{PTEN} and \textit{TP53} as well as by TRK and PI3K dysregulation.

The current biological knowledge was therefore summarised as follows: HGG in children harbour genomic profiles which distinguish them from HGG in adults. HGG in children appear to be preferentially and differentially driven by PDGFR signalling. "Paediatric HGG" would not be correctly defined as "HGG under 18 years of age", as HGG tumours in adolescents may behave more like those occurring in adults. Compared with all others, very young children (perhaps up to 3 years of age) have a different biology and clinical outcome. Finally, DIPG have a distinct biology from other, supratentorial HGG, and they may actually arise from a different cell type. Improved tumour models should be developed for paediatric HGG.

Recent publications on biology, pathology and models pertaining to paediatric HGG include: (Bax et al. 2010; Paugh et al. 2010; Bax, Gaspar, et al. 2009; Bax, Little, et al. 2009; Puget et al. 2011).
A further presentation provided comprehensive paediatric clinical HGG background information, including characteristics at the time of diagnosis and results of clinical trials, providing data for comparing paediatric and adult populations.

**Survey and discussion of neuro-oncology care for paediatric patients with HGG in Europe and considerations for paediatric HGG studies**

Summarised responses to the items of the questionnaire (see annex) and survey were presented and commented upon by participants. In total 25 responses (from 11 countries) had been received from 43 addressees (lead paediatric oncologists), who treat from 1 to 10 (median 4) paediatric patients with HGG per year. As such, the responses were considered to reflect the current standards of HGG care in children and its variability across Europe. However, almost no data or reasoning was provided with the responses so it is unknown how the respondents weighed any evidence.

Some items were discussed during the meeting with a view to exploring consequences for paediatric HGG study design and conduct, as indicated below:

- Diagnosis was always made using conventional contrast enhanced MRI, which in a large proportion of patients was augmented using diffusion MRI, dynamic contrast enhanced (DCE) MRI and MR spectroscopy (MRS), in order of decreasing frequency. An MRI to document baseline postoperative tumour status was obtained within 24 hours in a significant proportion of paediatric patients and in all patients within 72 hours after tumour surgery.

- Prognostic factors (at baseline, that is, after tumour surgery) with favourable impact are believed to be, in decreasing order, the achievement of near total resection, WHO histological grade III (that is, not glioblastoma/grade IV), age less than 3 years (compared to all other ages; adolescents with HGG may be an adult-like group) and tumour location (e.g., cerebral hemisphere vs. diffuse midline HGG). Half of paediatric oncologists at most responded that performance status or MGMT status are of prognostic value, but few responded that presence or absence of metastases or EGFR status are of prognostic value.

- For clinical decision making for an individual patient, radiological criteria to define a response were mostly based on Macdonald (D. Macdonald et al. 1990), WHO (e.g., as in Warren et al. 2001) or RECIST (Therasse et al. 2000). The majority of paediatric oncologists had seen pseudoprogression and most had explored this further using augmented MRI (see above) and rarely with PET techniques.

- In the case of newly diagnosed HGG: Half of the respondents considered the treatment of anaplastic astrocrytoma and anaplastic oligoastrocytoma (WHO grade III histology) to be different from that used for glioblastoma (WHO grade IV histology). For grade III as for grade IV gliomas, most paediatric oncologists institute (after tumour surgery), systemic chemotherapy with single agent temozolomide during and after radiation therapy (Stupp et al. 2005), but for a total duration of 12 months. For grade IV gliomas, a proportion of respondents also considered multi-agent systemic chemotherapy. In contrast, in younger children (e.g. less than 3 years of age), multi-agent systemic chemotherapy regimens like HIT-SKK (Rutkowski et al. 2005) or BBSFOP (Lafay-Cousin & Strother 2009) are used. During the discussion it was suggested that preferences for the choice of a particular comparator regimen in future clinical trials might be stronger in Europe than in the U.S. Cranial radiation therapy, as scheduled for newly-diagnosed older children and sometimes even for younger children at the time of progression or relapse, may interact with any experimental treatment administered; this has to be taken into account.
In the case of progression or relapse of HGG: Various treatment approaches were envisaged by the responding paediatric oncologists, including systemic chemotherapy regimens (e.g., PCV regimen, combinations of other drugs with irinotecan or etoposide, etc.) or experimental treatments (including small molecule inhibitors, anti-angiogenic agents, immunotherapy, antibodies).

A majority considered that paediatric patients with newly-diagnosed HGG could not be studied alongside those with HGG progression or relapse in a clinical trial, but no trial design details were discussed. With respect to the widely-accepted oncology development paradigm of first obtaining results of studies new agents in patients with HGG progression or relapse prior to running trials in treatment-naïve patients, opinions were split as to whether such results could be predictive of activity in patients with newly-diagnosed HGG.

Few respondents considered that patients with a diffuse intrinsic pontine glioma (DIPG) could be studied alongside patients with other HGG in a paediatric clinical trial, but a third responded that DIPG could be studied together with diffuse midline HGG. Similarly, they thought that studying patients with gliomatosis cerebri together with other HGG was an acceptable approach to take.

In paediatric patients with newly-diagnosed HGG, almost all responding paediatric oncologists believed that a randomised controlled trial would be the best study design, with the control arm containing temozolomide during and after radiation therapy (as above). Few considered that a single arm study design would be acceptable, but no further details were provided. During the discussion the lack of controlled data was highlighted; this deficiency also hinders the comparison between the results of adult and paediatric HGG studies, such as the seemingly divergent results in terms of response but possibly similar results in terms of the proportion of patients without progression after six months of treatment with bevacizumab (Gururangan et al. 2010; Narayana et al. 2010; Friedman et al. 2009).

In paediatric patients with a progression or relapse of HGG, a majority of respondents suggested a randomised controlled trial with two or three arms (experimental as single agent, experimental on top of a comparator treatment, comparator treatment, respectively; example: http://clinicaltrials.gov/ct2/show/NCT01236560). However, half of respondents also considered a single arm trial and comparisons with historical controls. During the discussion it was mentioned that historical data should in any case be used for planning paediatric studies. One register comprises data on the course of about 700 paediatric patients newly-diagnosed with HGG.

The appropriate efficacy endpoint in potential future randomised controlled trials in paediatric patients with newly-diagnosed HGG was variously regarded as being either the proportion of patients showing response, proportion of patients surviving 6 months or longer without progression, overall survival or (by more respondents) median progression-free survival time.

It was mentioned that criteria for the assessment of response (and for the assessment of progression) for paediatric HGG studies are currently been developed, complementary to recently published criteria (Response Assessment in Neuro- Oncology or “RANO” criteria) developed using data from studies with adults (Wen et al. 2010). Functional MRI parameters were considered an important part of the paediatric criteria. Response rate as such was not recommended based on experience with this endpoint in adult studies. One suggestion was that radiological criteria might depend on the mechanism of action of the medicine(s). Paediatric (neuro-) oncologists in Europe and in the U.S. are working together internationally and might pool data to help inform the development of relevant endpoints.
**Meeting outcome summary**

The following summary was given at the end of the meeting:

- The results of the questionnaire and survey as presented above should be taken into account for future paediatric HGG studies. Age itself does not define distinct subsets of paediatric patients with HGG, but biological characteristics are different between age groups and they may best explain clinical differences found between age groups. It is also essential to consider the patients' individual characteristics, in terms of clinical features, tumour biology and previous lines of treatment. Collaboration between adult and paediatric neuro-oncologists and representatives of other disciplines involved in the treatment of patients with HGG is highly desirable to achieve better future clinical studies. This collaboration should include translational scientists, in order to ensure prioritisation for investigating emerging information on tumour biology and novel targets.

- A paediatric development of an anticancer medicine for HGG should be guided by interesting activity and biological relevance, which might be driven more by information emerging from non-clinical pharmacology or paediatric molecular pathology/biology studies than studies in adult patients. It is therefore desirable to thoroughly investigate tumour samples from all paediatric HGG patients in clinical studies, ideally not only at diagnosis but also subsequently, e.g., at the time of relapse or progression, to further explore potential changes in tumour biology, resistance mechanisms etc. At this time, biological characterisation of paediatric HGG may provide hypotheses for oncogenesis and for the possible role of new treatments. Such data provides a rationale for clinical trials that are required to show that targeted treatments actually improve the prognosis of paediatric HGG. Paediatric trials in HGG necessitate central pathology review, setting up reference laboratories as well as validating biological assessments.

- The response criteria as set out in (Wen et al. 2010) can be used for paediatric studies in HGG at this time. The proportion of patients who do not have a progression six months after diagnosis (PFS6) may be a valid endpoint. However such binary endpoints have the highest sample size requirements, for example, compared to time-to-event endpoints. However, this endpoint may not be useful for cytostatic agents such as antiangiogenic medicines, where it cannot be reliably assessed. Overall survival instead of progression-free survival may be more appropriate. If progression is a clinically significant and tangibly adverse event for the individual patient, then freedom of progression may be a primary endpoint (in line with European guidance). Study designs which encompass an option to cross-over to another agent after disease progression may be helpful, depending on the availability and use of any other, active treatments. If overall survival is a primary efficacy endpoint, then the proportion of patients alive at twelve months (OS12) should be used, because at six months essentially all newly-diagnosed patients are expected to be alive.

- It is possible to conduct randomised controlled studies with paediatric patients with HGG. The opposing forces of small patient numbers and of the desirability of maximally robust data have to be carefully balanced. Study integrity and robustness will be supported by further design details, such as the choice of active comparator(s), the allocation concealment and the implementation of blinding including the possible use of placebo on top of standard of care. Ethical questions may arise related to study design details and related to knowledge quickly accumulating from studies in adults. They can be discussed at various levels, including at the time of PIP applications and with the EMA / PDCO.

- At this point, in the absence of a thorough discussion, the EMA / PDCO have not drawn firm conclusions from the expert workshop, but take the discussion into account and will continue to involve external experts in medicinal product-specific PIP evaluations. As foreseen by the European legislation for paediatric medicines (Regulation (EC) 1901/2006), existing data can and should be
submitted for regulatory assessment, whether from commercially or non-commercially sponsored studies.

The experts briefly mentioned that the following topics related brain tumours in children represent unmet needs for the treatment of these diseases but could not be addressed during this meeting:

- Any generally required parts of paediatric developments, such pharmaceutical measures, non-clinical studies, clinical dose-finding and paediatric-specific safety documentation.
- HGG in paediatric patients who by virtue of their young age are not routinely scheduled to receive radiation therapy as part of the treatment of a newly-diagnosed HGG (usually under 3 to 5 years of age; this varies depending on the availability of more focused radiotherapy technology)
- DIPG (diffuse intrinsic pontine glioma), for which it was recognised that developments of medicines should include a strong framework for collecting and analysing patient samples and biological data.
- Low-grade glioma (LGG)
- Central nervous tumour types other than glial tumours with significant therapeutic needs in the paediatric population: medulloblastoma and other PNET (primitive neuro-ectodermal tumour), ATRT (atypical teratoid rhabdoid tumour) and ependymoma.

Within the constraints of this teleconference, these subsets could not be addressed and an in-depth discussion of the general HGG questions was not possible. A follow-up meeting was recommended by the experts.

**Further steps**

- EMA to consider a follow-up meeting with the experts in order to hold a discussion that facilitates that explicit consequences for paediatric investigation plans (PIPs) in HGG can be drawn
- EMA to consider drafting a model HGG PIP
- Academic investigators to consider the possibility of a meta-analysis of existing paediatric academic databases from prior clinical trials in both newly diagnosed and recurrent/relapsed paediatric HGG to evaluate possible study end-points (i.e., response rate, progression-free survival and overall survival). The EMA offers scientific advice to support the qualification of novel methodologies and biomarkers.

**List of participants**


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References


