Chemotherapy response rates in recurrent/progressive pediatric glioma: results of a systematic review

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Authors' objectives
To present a systematic analysis of the currently available clinical data on chemotherapeutic management of recurrent childhood glioma.

Searching
The following sources were searched: MEDLARS from 1970 to September 1998, Cancerlit, EMBASE, and Current Contents (on CD-ROM). These were supplemented by manual searches of the bibliographies of relevant studies and reviews of relevant textbooks. The search was limited to publications in the English language. The literature retrieval methods are described in more detail elsewhere (see Other Publications of Related Interest nos.1-2).

Study selection
Study designs of evaluations included in the review
Published randomised (RCTs) and non-randomised clinical trials were included. Studies of animals and in vitro studies were excluded, as were review articles and published abstracts.

Specific interventions included in the review
The chemotherapeutics included high-dose cyclophosphamide, carboplatin, PCNU, INF-alpha, idarubicin, cisplatin, topotecan, AZQ, etoposide, ara-C, nitrogen mus., vincristine, procarbazine, prednisone, high-dose thio-tepa, etoposide, bone marrow transplant, busulfan, thio-tepa, ifosfamide, iomustine and melphalan. Patients were stratified into 6 distinct chemotherapy categories based on the frequency of drug use. The categories were platinum-based regimens, nitrosourea-based, cyclophosphamide or ifosfamide-based, etoposide-based, thio-tepa-based, and others. Studies of immunotherapy, photodynamic therapy and hyperthermia were excluded.

Participants included in the review
The participants were paediatric patients less than 21 years of age with recurrent gliomas. The histologies eligible for inclusion were glioblastoma, multiforme, anaplastic astrocytoma, brain stem glioma, ependymoma, oligodendroglioma and mixed oli-astrocytoma. Studies which included patient histologies other than glioma, e.g. medulloblastoma, were included only if the data on the patients with glioma could be extracted separately. Studies of pilocytic astrocytoma and cerebellar astrocytoma were not eligible for inclusion.

Outcomes assessed in the review
The primary outcomes of interest were tumour response rates, time to tumour progression (TTP), and overall survival (measured in weeks). The tumour response rates were classified as either complete response, partial response or stable disease.

How were decisions on the relevance of primary studies made?
The initial citations from the literature search were screened by a physician investigator to exclude those that did not meet the specified inclusion criteria. The publications were subsequently selected by two researchers, one of which was an oncologist.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
A data extraction form was designed for recording relevant data from each paper. Data were extracted for the following key categories: publication date and geographic location; patient demographics; treatment, e.g. type of chemotherapy used, steroid use, and degree of resection of primary disease; and clinical outcomes of interest, i.e. tumour response rates, TTP and overall survival. For each study, the mean difference between the treatment and control was calculated, and the pooled variance was estimated. Data were extracted by two researchers, one of which was an oncologist, and any differences were resolved by consensus.

Methods of synthesis
How were the studies combined?
If insufficient data were available for a formal meta-analysis, the outcome data were summarised across studies and stratified by drug treatment group. Data permitting, a meta-analysis was performed using a general variance method with a continuous measure of effect (fixed-effect model), and a 95% confidence interval was calculated for the summary mean (see Other Publications of Related Interest no.1). Descriptive variables and study characteristics were summarised for each study in tables, and summarised using descriptive statistics. General linear models and survival analyses were used to identify key variables having an effect on median survival and TTP. All data on median TTP and median survival were summarised over treatment arms using means. The summarised response rates were calculated and weighted by study sample size.

How were differences between studies investigated?
Heterogeneity was formally assessed using Q test for homogeneity. The outcome data were summarised across studies and stratified by drug treatment group.

Results of the review
Twenty-seven studies were included. These consisted of Phase 1 and 2 trials and retrospective case series; no RCTs met the specified inclusion criteria. There were a total of 576 patients in the 27 included studies. Only patients analysed for efficacy (n=574) were included in the calculation of the outcome measures of interest.

The lack of data precluded a formal meta-analysis. The total tumour response rates across drug classes ranged from 33.0 to 48.8%. The combined complete and partial response rates were generally less than half of the total response rates, and ranged from 10.4% for patients treated with thio-tepa-based regimens to 23.5% for patients treated with etoposide-based regimens. This indicated that much of the observed response was due to disease stabilisation.

Only 26% of the available trials contained information on overall survival. This precluded any meaningful analysis of this outcome measure.

Data on TTP were not detailed in 8 of the 27 studies (30%). For the remaining studies, the median TTP was 24.4 weeks (range: 14.0 - 120.4). The wide variation in TTP was partially attributed to differences in the tumour histologies across the included studies. The mean TTP values ranged from 26.7 (plus or minus 10.8) weeks for patients treated with cyclophosphamide-based regimens, to 49.7 (plus or minus 34.4) weeks for thio-tepa-based regimens. Due to the small number of patients in each study group, no significant difference in TTP was found across chemotherapy classes, with the exception of platinum- versus cyclophosphamide-based therapies (p<0.001). The most frequently used drugs were the platinum-based regimens, which demonstrated a mean TTP of 42.0 (plus or minus 23.4) weeks.

Authors' conclusions
The authors concluded that the drug classes discussed in the present review, with the exception of platinum analogues, have been used in relatively few clinical trials. This severely limits any definitive conclusions regarding response rates and, due to the lack of phase 3 trials, survival impact for any drug or drug category is unavailable. They also concluded that overall, the combined complete and partial response rates for chemotherapy in recurrent paediatric high-grade glioma ranged from approximately 10 to 20%, with a mean of approximately 14%. This is in contrast to the combined complete and partial response rates observed in adults with recurrent high-grade glioma, approximately 20 to 25% (see Other Publications of Related Interest no.2). Differences in tumour histology may partially account for such differences, e.g. a lack of patients with brain stem glioma in the adult database.
In terms of TTP, the data suggested that the platinum analogues may warrant further investigation, although the small number of patients in any of the drug classes makes definitive conclusions impossible.

**CRD commentary**
The review question was clearly stated. The literature search was comprehensive, although it was restricted to English language publications and only published trials were eligible for inclusion. The validity of the primary studies was not assessed. Study details were well reported and studies were summarised in an appropriate manner. However, publication bias was not assessed. Some details regarding the review process were reported, e.g. the number of reviewers who selected the publications and extracted the data, but some were missing.

The authors’ conclusions appear to follow from the results presented. However certain limitations, listed by the authors, prevented them from forming any definitive conclusions.

**Implications of the review for practice and research**
Practice: The authors did not state any implications for practice.

Research: The authors state that there is a great need for clinical trials to address the issue of chemotherapeutic management of recurrent glioma in children. These trials must have sufficient statistical power to detect differences in outcomes among various drug treatments. Given the poor clinical outlook for most children with this disease, such trials should be a major research priority.

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