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REVIEW

Temozolomide and oral etoposide in children with recurrent malignant brain tumors

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Abstract

Despite advances in the treatment of brain tumors, the prognosis of children with recurrent malignant brain tumors remains poor. Etoposide (VP-16), an inhibitor of nuclear enzyme deoxyribonucleic acid (DNA)-topoisomerase II, has shown activity in brain tumors. Its efficacy appears schedule dependent but, to date, the most effective schedule of administration has not been well defined. Temozolomide (TMZ), like VP-16, penetrates the blood–brain barrier and has activity against malignant brain tumors. This novel alkylating agent is rapidly absorbed and is highly bioavailable after oral administration. The antitumor activity of TMZ has been shown to be schedule dependent. Based on the evidence of different mechanisms of cytotoxicity, TMZ and VP-16 have been utilized in combination in patients with malignant brain tumors. This review evaluates the results derived from the combination use of TMZ and oral VP-16. The reported data suggest potential activity of oral VP-16 and TMZ alone or in combination. Further clinical trials are needed to explore and confirm their promising activity in relapsed brain neoplasms.

Keywords: etoposide, glioma, medulloblastoma, recurrent brain tumor, temozolomide.

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Introduction

Based on the 2016 World Health Organization's classification of tumors of the central nervous system (CNS), glial tumors or gliomas include astrocytomas, glioblastomas, diffuse midline gliomas, oligodendrogliomas, mixed tumors, or oligoastrocytomas.[1]

Glioblastoma multiforme and anaplastic astrocytoma constitute 15–20% of all pediatric CNS tumors and represent a therapeutic challenge for clinicians due to their resistance to curative treatment. The supratentorial hemispheres or the brainstem area are commonly involved by these malignant tumors. A multimodality approach, including neurosurgery, radiotherapy (RT), and chemotherapy (CT), is the common treatment reserved for children affected by supratentorial astrocytomas and aged more than 3 years.

Despite the adoption of a multimodality approach, the long-term outcome of patients affected by these tumors is still grim. Two-year survival rate is less than 30% for supratentorial tumors and less than 10% for most pontine gliomas.[2]

It should be noted that the therapeutic approach of children with high-grade glioma depends on the peculiar characteristics of these tumors at this specific age, first of all somatic histone mutations.

For example, a specific group of tumors, primarily occurring in children, is characterized by K27M mutations in the histone H3 gene *H3F3A*, or less commonly in the related *HIST1H3B* gene, encoding for histone 3 variants H3.3 and H3.1, respectively, which are considered hallmark events driving gliomagenesis. A further case is represented by the methylation of the MGMT gene promoter: MGMT promoter-methylated tumors appear to have a better response to alkylating agents when compared to MGMT promoter-unmethylated tumors. Mutations of the isocitrate dehydrogenase gene and tumor suppressor gene *TP53* represent novel indicators for the clinical outcome of children with malignant glioma by influencing their poor responsiveness to temozolomide (TMZ).[3,4]

The treatment of patients with malignant brain tumors remains challenging. The aim of our manuscript is to review the results derived from the combination use of TMZ and oral VP-16. For this purpose, we conducted a literature research of the MEDLINE PubMed database on articles published between 1980 and 2019 reviewing: "Temozolomide AND oral etoposide AND central nervous system tumo(u)r."

CNS tumors and treatment

The overall survival (OS) for patients with recurrent or progressive high-grade gliomas is extremely poor, with more than 80% of affected children dying within 24 months from diagnosis.[5]

The treatment is based at first on maximal safe surgical resection. Surgery is generally associated with RT in children with an age more than 3 years, whereas for young children aged less than 3 years, RT is postponed in order to preserve the developing brain from severe RT-related late effects. The role of adjuvant CT is unclear; so, whenever available, children can be enrolled in clinical trials with new antineoplastic agents.[4]

Wong and colleagues in their meta-analysis on the role of prognostic factors in recurrent gliomas reported an objective (complete response [CR] plus partial response [PR]) response rate of 9%, with a median progression-free survival (PFS) and a median OS of 10 and 30 weeks, respectively, from relapse.[6] In recurrent childhood gliomas, Huncharek and colleagues reported a systematic analysis of 27 nonrandomized clinical trials; a median overall response rate of about 14% and a time to progression from 29.4 to 49.7 weeks were found.[7] Tumors recurring locally, if feasible, can be approached with a complete re-excision. Conventional RT still remains a treatment modality for children who have not previously received RT. Stereotactic radiation therapy has been adopted in adults with high-grade gliomas, but its real role in achieving a local control in children with brain tumors is still unclear.[8] Radiosurgery, by delivering high dose-per-fraction treatments to small intracranial lesions, can play a key role in the treatment of unresectable, residual, or recurrent tumors previously treated with RT.[9] Unfortunately, the efficacy of antineoplastic compounds in patients with recurrent disease is negligible. Many phase II clinical trials adopting multiple new antineoplastic agents showed a marginal clinical benefit for this setting of patients.[10–14]

Medulloblastoma (MB) is the most common malignant brain tumor.[15] Standard treatment consists of surgery aimed to excise as much tumor as possible followed, except for young children aged less than 3 years, by whole neuraxis RT. MB is clearly a chemosensitive tumor with several phase II studies showing chemotherapeutic activity in relapsed tumor, but the vulnerability of the immature CNS of that population to neurotoxic therapy can negatively impact on treatment.[5,16–23]

Children with MB are generally stratified into "standard risk" and "high risk" categories based on the presence of metastases and volume of postoperative tumor. In average-risk patients older than 3 years, the treatment involves surgery and adjuvant RT followed by CT. In high-risk patients older than 3 years, the treatment involves surgery, RT with concomitant CT, followed by CT. Whereas, in infants and children less than 3 years of age, the treatment includes surgery and CT.[16]

The benefit of pre- and/or post-CT in nonmetastatic MB is accepted by several international groups. However, this benefit in terms of improving survival is yet to be fully established in terms of results from randomized clinical trials. Likewise, in metastatic MB, the addition of CT to RT seems to increase the survival rate.[24] Although many children treated for MB can have long survival, 30–50% of them will relapse with an almost inevitably fatal disease.[25,26]

Children with relapsed MB carry a poor prognosis, especially when the relapse occurs after conventional RT, and only few long-term survivors are reported following additional treatments, including surgery, RT, and CT. The few reports on long-term survivors with recurrent MB have a median survival less than 1 year.[27]

Data from the Children's Hospital of Philadelphia on 23 children with recurrent MB showed a poor outcome: the median survival was 5 months and the longest survivor was 28 months from relapse.[28]

Similar data were registered in patients by the Stanford University Medical Center: no long-term survivors with relapsed MB were noted.[29] Finally, among 46 children with recurrent MB treated according to Société Française d'Oncologie Pédiatrique (SFOP) protocols M7, M8, or M9, only one was cured and alive.[30]

Etoposide

Etoposide (VP-16), an inhibitor of the catalytic cycle of deoxyribonucleic acid (DNA)-topoisomerase II, is an antineoplastic agent adopted for the treatment of multiple brain tumors. Its efficacy appears schedule dependent but, to date, the most effective schedule of administration has not been well defined. The optimum route of administration and dosing schedule for VP16 have been exhaustively investigated. Infusional (intravenous and intra-arterial), oral, and even intrathecal administrations have been compared in the treatment of advanced malignancies, including breast, lung, ovarian, and soft tissue sarcoma as both a first-line and salvage regimen.[31–36]

Data from pharmacological studies have shown that a prolonged administration schedule of VP-16 can enhance the cytotoxic activity of the drug and, similar to the intravenous administration, the oral dosing is able to achieve the equivalent cytotoxic effect.[37–40] In addition, when a prolonged administration schedule is adopted, there is an inhibition of the repair of DNA breaks by cancer cells due to the prolonged topoisomerase II blockage.[41]

The efficacy and relative safety of prolonged administration of oral VP-16 have been demonstrated as monotherapy in the treatment of many cancers, including lung and breast cancers.[40–46]

It has also been used successfully in combination with other antineoplastic agents, including cisplatin and carboplatin or additionally combined with ifosphamide, 5-fluorouracil, paclitaxel, or vincristine.[32,47–57]

Based on the results of multiple clinical studies, small repeated doses of VP-16 appear to have a higher response rate than a single large dose.[37] In addition, clinical responses to daily oral dosing of VP-16 are registered also in patients with

tumors resistant to a short course (5 days) of VP-16 given intravenously.[58]

With regard to brain tumors, Relling and colleagues showed that a daily oral dose of at least 50 mg/m^2 is required to achieve adequate cytotoxic concentrations into the cerebrospinal fluid compartment.[59]

With regard to the risk of secondary leukemia or myelodisplastic syndrome after treatment with VP-16, data available suggest a potential increased risk especially for patients receiving a high cumulative dose (i.e. >6 g/m^2) or continuous administration (i.e. 21 consecutive days out of 28).[60,61]

VP-16 treatment monotherapy has been adopted both for children and adult patients with brain tumors.

Chamberlain and colleagues observed marginal toxicity and significant response rates of 50–63%, with responses lasting up to 8 months, when VP-16 was given orally over a prolonged period as salvage therapy in children and young adults suffering from relapsed or recurrent MB and low-grade gliomas.[62–66] Similar results have been reported by other authors in a small series of patients with ependymomas and pediatric gliomas.[57,67]

In the Chamberlain studies, the authors emphasized that in children with recurrent nondisseminated intracranial ependymoma and who are resistant to surgery or other CT strategy, VP-16, administered orally and chronically, was well tolerated.

In a series of 12 patients, Chamberlain registered 2 PRs, 4 stable disease (SD), and 6 progression disease (PD) with a scheme of VP-16 orally administered at 50 mg/m^2/day for 21 consecutive days with a 14-day interval followed by an additional 21 consecutive days of oral VP-16.[68]

Of interest is a study by Pajtler and colleagues on the safety of the intraventricular VP-16 administration in patients with refractory or recurrent malignant brain tumors.[69] Objective responses were reported in recurrent MB with schedules of oral VP-16 50–60 mg/m^2/day for 21 days as well as 50 mg/m^2/day for 10 days.

Ashley and colleagues demonstrated the efficacy of the same schedule in 6 out of 7 patients with recurrent MB67 all previously treated with intravenous VP-16. Also, Needle and colleagues obtained a PR in 3 of 4 patients with primitive neuro-ectodermal tumor (PNET)/MB.[58]

Efficacy has also been reported by Schiavetti and colleagues adopting a 10-day schedule oral VP-16 in two children with MB (a CR and a PR, respectively).[70] For all these schedules, the VP-16 orally administered was well tolerated and the acute toxicity mild.

Perez-Somarriba and colleagues also demonstrated the success of treatment with etoposide in some cases of relapsed MB.[15] In their phase II trial in children with newly diagnosed high-risk MB, Esbenshade and colleagues obtained an improvement, compared with the standard treatment, of the PFS and OS for these patients adopting an intensive protocol including oral VP-16. Patients were stratified into two groups based on the VP-16 dosage: 50 versus 35 mg/m^2/day during RT. Both groups then received, as adjuvant CT post-RT, cycles of cisplatin/oral etoposide and cyclophosphamide/vincristine. These results underline the need for evaluation of this treatment in larger trials to obtain more data about its toxicity before it can be adopted as standard therapy.[71]

Temozolomide

TMZ is an alkylating antineoplastic drug that has shown promising activity in patients with malignant gliomas.[72–76] TMZ belongs to the second-generation of imidazotetrazine prodrugs: their degradation at physiologic pH determines the formation of the cytotoxic monomethyl 5-triazeno imidazole carboxamide (MTIC). MTIC performs its antitumoral activity by adding methyl residues to the N^7-methylguanine, N^3-methyladenine, and O^6-methylguanine nucleotides in the DNA molecule.[72,73]

Following oral administration, the bioavailability is approximately 100% within 2 hours after its administration due to the rapid adsorption. TMZ is able to cross the blood–brain barrier so it was of interest for the treatment of CNS neoplasms. Its first use was in early clinical trials enrolling patients with malignant high-grade gliomas. The activity of TMZ was established by two pivotal studies in adult patients with recurrent anaplastic astrocytoma and glioblastoma; notably, the treatment was well tolerated with minimal side effects.[72,73]

TMZ has demonstrated efficacy when utilized with lomustine as adjuvant therapy after TMZ plus RT for the therapy of pediatric high-grade gliomas.[77] The antitumor activity of TMZ appeared to be schedule dependent, and TMZ achieved higher response rates when the total dose was administered over 5 days.

Estlin and colleagues in their phase I trial enrolling children with high-grade astrocytomas defined the TMZ maximum-tolerated dose: 200 mg/m^2 once daily for 5 consecutive days was the recommended dose for phase II studies in children who have not previously treated with cranio-spinal irradiation or nitrosurea-based CT.[78]

Adopting that recommended dose for the following phase II clinical trial in pediatric patients with relapsed or progressive high-grade astrocytomas, the United Kingdom Children's Cancer Study Group (UKCCSG)/SFOP group reported a response rate of 12 and 6% for supratentorial high-grade and brainstem gliomas, respectively.[79]

Vershuur and colleagues studied 20 children with recurrent high-grade gliomas as a single institution experience at the Institut Gustave Roussy. They reported an overall response rate of 20% (1 very good partial response (VGPR) and 3 PR) and a median survival up to 10 months.[80] Eleven patients reported an improvement of their clinical status, and almost 50% of them could decrease or stop corticosteroids. In an Italian phase II study

enrolling 24 children with recurrent or relapsed high-grade glioma (including 7 brain stem tumors), TMZ showed only a marginal activity. No CR or PR was observed, and SD was the best response. Steroid withdrawal was not possible in any patient, and a reduction of steroid dosage was obtained in three patients.[81]

Rizzo and colleagues demonstrated that RT plus TMZ did not lead to a better disease-free survival than RT alone, though OS was greater than in other studies, demonstrating that RT plus TMZ may affect survival.[82]

Chiang and colleagues evaluated the efficacy of TMZ and RT in patients with diffuse brainstem gliomas. Patients were divided into two groups: the first one received RT alone followed by TMZ, and the second RT and concomitant TMZ 75 mg/m^2/day followed by further cycles with TMZ. In both groups, there was no CR to RT, and all patients experienced disease progression. Therefore, TMZ in addition to RT did not produce better results than RT alone.[83]

In an American phase I study of TMZ in pediatric tumors, three objective responses after two cycles were observed (1 supratentorial PNET, 1 MB, and 1 malignant glioma).[84]

In an Italian cooperative study on children with relapsed and/or refractory MB, TMZ showed a significant activity with a response rate (CR + PR) of 48.6% (personal data). With regard to toxicity, grade 3–4 thrombocytopenia and grade 3–4 neutropenia were registered in 32 and 18% of the total 28 cycles, respectively.[85]

Unfortunately, the hypermethylation status of the MGMT gene promoter region appears to affect the efficacy of TMZ in adult patients with glioblastoma: the MGMT gene promoter methylation has been reported as the strongest predictive factor of survival in patients with glioblastoma. The potential impact of this evidence for childhood high-grade gliomas is not yet completely clear.[3]

Ridola and colleagues evaluated the influence of MGMT status on treatment efficacy. They evaluated the adoption of a metronomic administration: that is, 21 days dosing TMZ 70 mg/m^2/day with a 7 days' break schedule. The administration of CT at a lower dosage and longer duration obtained a complete or partial inhibition of the enzyme MGMT in contrast to the 5-days administration schedule. In addition, a higher cumulative dose was achieved with metronomic CT without increasing the toxicity profile, mainly represented by lymphocytopenia.[86] Cefalo and colleagues studied the clinical efficacy of TMZ in children with high-grade astrocytomas and relapsed MB.[87] For the 40 patients treated, the results were: 6 CR, 11 PR, 10 SD, and 13 PD. Responses to TMZ were registered at a dosage of 120 mg/m^2/day with tolerable toxicity. The disease-free survival and OS at 6 and 12 months were 30 and 7.5% and 42.5 and 17.5%, respectively. By comparison, in patients who obtained an objective response, the disease-free survival and OS at 6 and 12 months were 70.6 and 17.5% and 94 and 41.2%, respectively. In addition, it was noted that 3-times-a-day administration, unlike single-dose administration, was associated with longer-lasting inhibition of the MGMT enzyme.[87]

In the case studies reported by Wang and colleagues on eight patients with recurrent embryonal tumors, TMZ 150–200 mg/m^2/day was administered for five consecutive days every 28 days. All children had received prior surgery, craniospinal RT and CT. The use of TMZ was of clinical benefit in 4 out of 8 patients, and the disease-free progression was 15.7 months.[88] Finally, Gururangan and colleagues evaluated the TMZ activity in progressive low-grade gliomas.[89] The drug was administered at a dosage of 200 mg/m^2/day for five consecutive days every 28 days. Disease-free survival at 2 and 4 years was 51 and 17%, respectively. OS at 2 and 4 years was 97 and 71%, respectively. These results underline the importance of considering TMZ as second-line treatment in children with nonresponsive low-grade glioma.

Etoposide and temozolomide combination

The oral VP-16–TMZ combination was designed to identify whether there is potentially an increase in the therapeutic index by TMZ and VP-16 in treating children with recurrent malignant brain tumors.

Recently, the activity of TMZ combined with oral VP-16 for children and young adults with recurrent malignant astrocytomas has been reported.[90] In the analysis, 11 patients received different combinations of TMZ (150–210 mg/m^2/day for 5 days) and oral VP-16 (50 mg/m^2/day for 4–12 days). All patients were previously treated with RT, and seven patients received CT. In total, 1 CR and 6 PR were observed.

Ruggiero and colleagues have evaluated CT with VP-16 and TMZ in patients with recurrent or progressive MB/PNET.[91] The objective responses registered for both drugs given simultaneously were better than the use of the two drugs separately. Among the 14 patients enrolled, 1 CR and 1 PR were noted. In another study, Ruggiero and colleagues analyzed the response rate to oral VP-16-TMZ in children with malignant glial tumors. The best response was the stability of the disease; neither CR nor PR was found.[92]

In conclusion, an appealing practice may be derived from the combination of a DNA alkylating agent with an inhibitor of the topoisomerase enzyme taking into account that the topoisomerases are essential to activate the DNA repair mechanisms following DNA alkylation. TMZ might enhance the recruitment of the topoisomerases by methylating the O^6 position of guanine: the final result is a theoretical enhancement of the topoisomerase inhibitor activity.[93]

Conclusions

The reported data suggest a potential activity of oral VP-16 and TMZ alone or in combination. Taking into account their favorable pharmacokinetic profile, oral administration, marginal toxicity, and the responses registered in different malignant brain tumors, further clinical trials are needed to explore and confirm their promising activity in relapsed brain neoplasms.

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