Biomedical & Pharmacology Journal, March 2020. Vol. **13**(1), p. 417-422

Efficacy of Temozolomide in Children with Solid Tumors

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http://dx.doi.org/10.13005/bpj/1901

(Received: 20 January 2020; accepted: 19 March 2020)

Temozolomide, an alkylating drug first adopted to treat patients with malignant gliomas, is actually an antineoplastic drug used in various regimens against childhood tumors. Treatment with temozolomide is an effective therapy for different childhood tumor types: brain tumors, neuroblastomas, Ewing's sarcoma, and rhabdomyosarcomas. Temozolomide has been used both as monotherapy and in polychemotherapy in combination with epipodophyllotoxins, camptothecin analogues, platinum compounds, vinca alkaloids and radiotherapy. The present study analyzes the treatment schedules including temozolomide in different cancer pathologies by comparing the results, in order to evaluate the efficacy of each treatment modality.

Keywords: Temozolomide, Children, Solid tumors.

The use of Temozolomide (TMZ) for the chemo-treatment of childhood malignancies has been larger than adults as it actually adopted in different malignancies other than brain tumors[1-2].

The purpose of the present manuscript is to describe the main pharmacological and clinical features of TMZ with a focus on its efficacy in children with solid tumors.

Pharmacological features

TMZ is a cytotoxic drug belonging to the class of alkylating agents. The alkylating chemotherapeutics have the property of forming highly reactive carbocations intermediate that create covalent bonds with sites rich in electron density, such as phosphate, amine, sulfhydryl and hydroxyl groups[1,3].

Consequently, their therapeutic and cytotoxic effects depend on the alkylation of reactive amines, oxygens and phosphates present in DNA. The precise cause of cell death associated with DNA damage is not known: cellular responses include cell cycle arrest and DNA repair attempts.

Specifically, TMZ is included in the triazene group and acts following its spontaneous, non-enzymatic activation in the methyl-triazeno-imidazol-carboxamide metabolite (MTIC) and kills the cells in all phases of the cell cycle.

TMZ is administered orally and has a bioavailability approaching 100%. Its half-life is 1-2 hours, while its main metabolite, MTIC, reaches peak plasma concentration (150 ng / ml) 90 minutes after administration and has a half-life of 2

hours. TMZ is not metabolized by the cytochrome P450 so it can be administered without risk of interaction with the common antiepiletic drugs[4,5,6].

In urine it is possible to find a small amount of unchanged drug or its main urinary metabolite, imidazole carboxamide, which is inactive.

The toxicity includes nausea, vomiting, myelosuppression, with leukopenia and thrombocytopenia (modest and reversible in 1-2 weeks), myelodysplastic syndrome, flu-like syndrome[7].

The less common adverse effects include liver toxicity, alopecia, flushing of the face, neurotoxicity and dermatological reactions. Following prolonged administration of TMZ, a greater risk of infection with Pneumocystis carinii has been reported; so, prophylaxis with co-trimoxazole during treatment and up to 3 months from its interruption is recommended[1,3,8].

TMZ in adults

TMZ is the first choice drug for the chemotherapic treatment of adults with high-grade gliomas and is largely used following surgery in combination with radiotherapy (RT)[9,10,11].

However, *Chamberlain* highlights how TMZ used in the treatment of high-grade gliomas has palliative and non-curative efficacy. It is evident that treatment with TMZ results in a modest increase in survival when compared to radiotherapy alone or to the administration of other alkylating agents such as procarbazine. Specifically, TMZ results in an increase in survival of 2.5 months, for an average overall survival of 14.6 months. This result is determined by the resistance to chemotherapy that high-grade gliomas present, caused by the overexpression of the DNA repairing enzyme O-6-Methylguanine-DNA Methyltransferase (MGMT). The expression of the MGMT enzyme is an index of the degree of methylation of the promoter region of the MGMT gene: a hypomethylation of the promoter correlates to a gene overexpression and therefore to a drug resistance. Secondary resistance is instead determined by exposure to alkylating agents and takes the form of mutations in DNA repair systems or in the selection and growth of tumor cell clones characterized by primary resistance mechanisms[3].

TMZ in childhood tumors

Brain tumors

TMZ has been mainly utilized for the treatment of embryonal brain tumors (medulloblastomas, primitive supratentorialneuroectodermal tumors - PNET, atypical rhabdoidteratoid tumors, ependymoblastomas and medulloepiteliomas)[12,13].

In the case-studies reported by *Wang et al.* it was highlighted that out of 8 patients suffering from embryonal tumors, treated primarily with surgery followed by cranio-spinal radiotherapy and chemotherapy and in which there was a recurrence of the disease, the use of TMZ obtained an advantage in 4 out of 8 patients with a mean disease-free progression (PFS) of 15.7 months. The drug was administered at a dosage of 150-200 mg/sqm/day for 5 consecutive days every 28 days[14].

In their study, *Cefalo et al*., evaluated the response to TMZ in children with high grade gliomas and recurrent medulloblastomas. The daily TMZ dose was divided into three daily administrations for 5 days every 28 days and, specifically: patients who have previously received treatment with high doses of chemotherapy and peripheral blood stem-cell rescue received a dose of 120 mg/sqm/day, which is then increased at 150 mg/sqm/day if there are no side effects; patients who have received cerebrospinal irradiation without high-dose chemotherapy received a dose of 180 mg/sqm/day; patients who have not previously been treated either with chemotherapy or with high-dose chemotherapy receive an initial treatment dose of 200 mg/sqm/day. For the 40 patients treated, the results obtained were: 6 complete response (CR), 11 partial response (PR), 10 stable disease (SD), and 13 progression disease (PD). Progression-free survival (PFS) for all patients at 6 and 12 months was 30% and 7.5%, respectively, The average overall survival (OS) at 6 and 12 months was 42.5% and 17.5%, respectively. Instead, among patients who had an objective response, disease-free survival at 6 and 12 months was 70.6% and 17.5% respectively, while the average overall survival at 6 and 12 months was 94% and 41.2%. On the basis of this treatment it was observed that responses to TMZ were obtained even at a dosage of 120 mg/sqm/day with a tolerable degree of toxicity. Furthermore, administration 3 times a

day was associated with a more lasting inhibition of the MGMT enzyme, since once-a-day dosing was associated with a greater ability to reactivate the MGMT enzyme[15].

TMZ has been also used in the context of a combination with oral etoposide. In the study of *Ruggiero et al.* the combination TMZ and oral etoposide for medulloblastomas and PNETs has been evaluated. The schedule TMZ 150 mg/sqm/day for days 1–5 and VP-16 50 mg/sqm/day for days 1–10 has been repeated every 28 days for a maximum of 12 cycles. The objective responses obtained were 1 CR and 1 PR among the 14 patients treated. However, the risk of second malignant diseases related to this combination therapy should be taken into consideration[8]. The combination TMZ and oral etoposide has been also utilized for malignant glial tumors. *Ruggiero et al*. reported only a marginal advantage from the association of an alkylating drug and a topoisomerase inhibitor, namely TMZ and etoposide. Regarding the response to therapy, the best response was represented by the stability of the disease; no CR or PR have been reported[16].

In the study of *Gururangan et al*. the role of TMZ in the treatment of progressive low-grade gliomas, mainly of the optic pathway, was evaluated[17]. Previous treatment included commonly first-line and second-line chemotherapy based on vincristine, carboplatin, etoposide, and vinblastine[18,19,20].

TMZ was administered at a dose of 200 mg/sqm/day for 5 days every 28 days. The results showed a PFS at 2 and 4 years of 51% and 17% and an OS at 2 and 4 years of 97% and 71%, respectively. Out of 30 patients treated, 2 PR, 12 SD, 1 MR, and 15 PD were registered. The toxicity was negligible[17].

Ridola et al. evaluated the role of methylation of the MGMT promoter in different treatment schedules. Limited efficacy has led to different patterns of administration. Based on the concept of metronomic therapy, the administration was evaluated for 21 days, with a 7-day break. The use of a chemotherapy cycle at a lower dosage, but of longer duration has shown a complete or partial inhibition of the enzyme MGMT. In patients treated with the 21-days schedule, greater inactivation of the MGMT enzyme was demonstrated with consequent reduction in drug resistance and inhibition of tumor angiogenesis. According to this rationale, TMZ was administered orally at a dose of 70 mg/sqm/day for 21 days every 28 days in children with ependymomas and gliomas. Some patients received concomitant radiotherapy with chemotherapy treatment. The results showed 2 PR, 14 SD, and 1 PD. Furthermore, by adopting this schedules a higher cumulative dose was administered without increasing the risk of toxicity[2].

Neuroblastoma

TMZ has been initially utilized for the treatment of neuroblastoma as monotherapy. In the *Rubie et al.* phase II trial, TMZ has been administered at a dose of 200 mg/sqm/day for 5 consecutive days every 28 days in 25 patients. Ten objective responses (CR + PR + MR) with mild/moderate toxicity were reported[21].

However, TMZ is more frequent used in combination with other antineoplastic drugs such as Topotecan (TOTEM). In 38 children with relapsed or refractory high-risk neuroblastoma, *Di Giannatale et al*. reported: 3 CR, 6 PR, 4 MR, 17 SD, 8 PD. The PFS at 12 months was 42% and 58%, respectively. On the basis of these results, therefore, TOTEM treatment appears as a rescue treatment in children with advanced neuroblastoma[22].

In the study by *Kushner et al.* the TMZ plus irinotecan therapeutic regimen was evaluated in 19 children with relapsed or therapy-refractory neuroblastomas. Specifically, the therapy included irinotecan intravenously for one hour in a dose of 50 mg /sqm/day and TMZ orally 150 mg/sqm/day for 5 days. The response to treatment was: for the 9 patients who had an incomplete response to induction therapy: 1 CR, 4 OR, 4 SD; for the 10 patients with incomplete response to rescue therapy performed after relapse: 1 CR, 3 OR, 6 SD[23].

In patients with topotecan-resistant neuroblastoma, the HD-CIT schedule (high dose carboplatin-irinotecan-TMZ) can be applied. According to the study by *Kushner et al.*, administration of the HD-CIT schedule can be performed in patients who have not previously been exposed to irinotecan and/or TMZ using the following dosages: carboplatin 1000 mg/sqm, irinotecan 250 mg/sqm and TMZ 1250 mg/sqm. Objective responses in 17 out of 25 evaluable patients were registered[24].

Ewing sarcoma

TMZ has been utilized for the treatment of Ewing's refractory sarcoma in combination with irinotecan (TEMIRI). In the study carried out by *Casey et al.,* out of 19 patients with evaluable disease, 5 CR, 7 PR, and 7 PD were recorded[25]. The same efficacy rate was reported by *Kurucu et al*[26].

Rhabdomyosarcoma

In the context of the treatment of relapsed rhabdomyosarcoma, the TMZ monotherapy has shown marginal activity while the association of TMZ, vincristine and irinotecan (VIT), is much more satisfactory. *Setty et al*. in their study with the VIT reported an overall clinical benefit rate (CR + PR + SD) of 26.7%[27].

TMZ and radiotherapy

In the *Sirachainan et al*. study TMZ-based therapy and radiotherapy were utilized for the brainstem intrinsic diffuse gliomas, followed by adjuvant treatment based on TMZ and cis-retinoic acid.

During RT (55.8-59.4 Gy fractionated into 31-33 doses over 6-6.5 weeks) patients received concomitant TMZ at a dose of 75 mg/sqm/day for 6 weeks.

Two weeks after completion of this first cycle patients received TMZ at a dose of 200 mg/sqm/day for 5 days and cis-retinoic acid at a dose of 100 mg/sqm/day for 21 days in a 28-day cycle. Following the TMZ+RT scheme, 7 PR, 4 SD, and 1 PD were registered. The EFS at 1-year was 41.7% ± 14.2% with a mean progression time of 10.2 ± 3 months; OS at 1-year was 58% ± 14.2% with a mean survival time of 13.5 ± 3.6 months[28].

In the *Chiang et al*. study, patients with diffuse brainstem gliomas were divided into 2 groups: the first group in which the RT was followed by chemotherapy with TMZ (RT plus TMZ); the second group received RT and concomitant TMZ 75 mg/sqm/day followed by chemotherapy with TMZ (CCRT+TMZ).

In the group receiving RT + TMZ treatment, out of 10 patients, 2 PR, 1 MR, 6 SD, and 1 PD were reported. In the group receiving CCRT + TMZ treatment, out of 8 patients were registerted 2 PR, 3 SD, and 3 PD.

All patients presented disease progression: for the RT plus TMZ group EFS was 7.4 months, while in the CCRT plus TMZ group the EFS was 6.4 months.

Based on these results, the addition of TMZ to RT did not seem to obtain an improvement for the prognosis of patients affected by brainstem gliomas[29].

A similar result was observed by *Rizzo et al*.: TMZ was administered with concomitant RT at a dose of 75 mg/sqm/day and then at a dose of 200 mg/sqm/day for 5 days every 28 days starting 4 weeks after radiotherapy,and for 12 cycles.

The results of this study showed disease progression and death of 13 out of 15 patients in a 15-month follow-up, while 2 patients remained alive with disease progression.

For all patients, except one patient who died during radiotherapy treatment, disease progression occurred during adjuvant TMZ treatment.

The EFS was 7.15 months, while OPS was 15.6 months. Therefore, the study showed that the TMZ plus RT treatment did not result in better disease free survival than radiation treatment alone[30].

CONCLUSIONS

TMZ is a drug of great importance in the treatment of different childhood cancers, especially in those patients who have not responded to the first-line treatment. The therapeutic schedules adopted are different and both the monotherapy and polychemotherapy have obtained significant clinical results in a wide range of tumors.

Based on the results obtained, TMZ may be a reasonable option to offer patients as salvage therapy.

ACKNOWLEDGMENTS

This work was supported by "Sara un angelo con la bandana Onlus"

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