

Phase II study of irinotecan in combination with temozolomide (TEMIRI) in children with recurrent or refractory medulloblastoma: a joint ITCC and SIOPE brain tumor study

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Background. This multicenter phase II study investigated temozolomide + irinotecan (TEMIRI) treatment in children with relapsed or refractory medulloblastoma.

Methods. Patients received temozolomide 100–125 mg/m²/day (days 1–5) and irinotecan 10 mg/m²/day (days 1–5 and 8–12) every 3 weeks. The primary endpoint was tumor response within the first 4 cycles confirmed ≥ 4 weeks and assessed by an external response review committee (ERRC). In a 2-stage Optimum Simon design, ≥ 6 responses in the first 15 evaluable patients were required within the first 4 cycles for continued enrollment; a total of 19 responses from the first 46 evaluable patients was considered successful.

Results. Sixty-six patients were treated. Seven responses were recorded during stage 1 and 15 in the first 46

ERRC evaluated patients (2 complete responses and 13 partial responses). The objective response rate during the first 4 cycles was 32.6% (95% confidence interval [CI], 19.5%–48.0%). Median duration of response was 27.0 weeks (7.7–44.1 wk). In 63 patients evaluated by local investigators, the objective response rate was 33.3% (95% CI, 22.0%–46.3%), and 68.3% (95% CI, 55.3%–79.4%) experienced clinical benefit. Median survival was 16.7 months (95% CI, 13.3–19.8). The most common grade 3 treatment-related nonhematologic adverse event was diarrhea (7.6%). Grade 3/4 treatment-related hematologic adverse events included neutropenia (16.7%), thrombocytopenia (12.1%), anemia (9.1%), and lymphopenia (9%).

Conclusions. The planned study primary endpoint was not met. However, its tolerability makes TEMIRI a suitable candidate chemotherapy backbone for molecularly targeted agents in future trials in this setting.

Keywords: medulloblastoma, temozolomide, TEMIRI.

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Medulloblastomas are aggressive embryonal tumors and represent the most common malignant pediatric brain tumors.^{1,2} Standard treatment includes surgery, craniospinal radiotherapy, and chemotherapy. Despite current multimodal treatment, prognosis remains poor, particularly in patients with recurrent or metastatic disease.^{1,3} The various therapeutic options, including high-dose chemotherapy, in patients who experience a relapse after craniospinal irradiation have unfortunately led to only minimal increments in progression-free survival.^{4,5} In the last 20 years, very few new chemotherapy agents have been incorporated into the therapeutic armamentarium in this setting. However, several drugs or drug combinations have shown moderate efficacy in phase I and phase II studies of recurrent disease.⁶⁻¹⁰ Indeed, the identification of treatment combinations that provide high response rates in these patients might also prove useful during the initial treatment of the disease.

Temozolomide was reported to be tolerable, demonstrating activity as a single agent in patients with pediatric malignant glioma¹¹ and in children and adolescents with recurrent or relapsed brain tumors, including medulloblastoma,^{10,12-15} or in combination with etoposide or O⁶-benzylguanine in the same treatment setting.^{7,8,16} Irinotecan has demonstrated activity in pediatric patients with relapsed or refractory solid tumors, including medulloblastoma.^{9,17-19} The combination of temozolomide with irinotecan (TEMIRI) is an attractive treatment option, firstly, because of the different toxicity profiles associated with the individual drugs and, secondly, due to the potential for a synergistic effect on efficacy from their combined activities. For example, tumors with DNA mismatch repair pathway deficiency are usually resistant to alkylating agents but are extremely sensitive to topoisomerase I inhibitors.²⁰ Moreover, O⁶ alkylation of guanine, a direct effect of the inhibition of O⁶-alkylguanine-DNA transferase (MGMT) by temozolomide, induces the formation of more topoisomerase I-DNA complexes, thereby increasing the cytotoxicity of topoisomerase I inhibitors.^{21,22} A synergistic effect on efficacy was demonstrated for the treatment combination in xenograft models where the antitumor activity of TEMIRI was significantly greater than that of either agent alone and was found to be independent of tumor MGMT expression.^{23,24} In clinical studies, TEMIRI demonstrated tumor responses in patients with adult malignant glioma^{25,26} and in childhood tumors, including neuroblastoma²⁷ and Ewing's sarcoma.^{28,29} Furthermore, gastrointestinal and hematologic adverse events (AEs) reported in these studies were tolerable.

This large phase II international multicenter study aimed to assess the activity and safety profile of TEMIRI in pediatric patients with recurrent or refractory medulloblastoma.

Materials and Methods

Eligibility

Patients were aged 6 months to ≤ 18 years with refractory medulloblastoma in which current standard treatment

approaches had failed. Other major inclusion criteria were: measurable primary and/or metastatic disease (at least 1 bidimensionally measurable lesion [at least 1 diameter >10 mm] on MRI); no previous treatment with temozolomide or irinotecan; Lansky-Play scale $\geq 70\%$ or Eastern Cooperative Oncology Group performance status ≤ 1 as appropriate based on age; life expectancy ≥ 3 months; and adequate organ function.

Patients could not be included if they had received chemotherapy during the previous 3 weeks or radiotherapy or nitrosoureas during the previous 6 weeks or had uncontrolled diarrhea; a serious concomitant systemic disorder; galactose, lactose, fructose, or glucose intolerance; hypersensitivity to irinotecan, temozolomide, or any of the excipients; and chronic inflammatory bowel disease and/or bowel obstruction.

The study was conducted in accordance with the Declaration of Helsinki and in compliance with International Conference on Harmonisation good clinical practice guidelines and local regulatory ethics committee guidelines. Written informed consent was required from parent(s) or legal guardian(s) and the patients, as appropriate, prior to study enrollment.

Study Design

This was a multicenter, single-arm, open-label phase II study with a 2-stage Optimum Simon design³⁰ to investigate irinotecan in combination with temozolomide in children with recurrent or refractory medulloblastoma. According to previous data showing delayed responses with temozolomide in pediatric brain tumors, including medulloblastomas,^{10,31} the primary endpoint was an objective tumor response during the first 4 cycles of treatment, which must have been confirmed by a follow-up objective tumor response assessment obtained ≥ 4 weeks after the initial documentation and was based on assessment by an external response review committee (ERRC). Secondary endpoints included confirmed best overall tumor response (within the first 4 cycles or any time on treatment) based on local investigator assessment, duration of tumor response, time to tumor progression (TTP), time to treatment failure (TTF), and overall survival (OS). The safety profile of TEMIRI was also investigated.

Treatment

Patients received oral temozolomide 100 mg/m²/day on days 1-5 followed by i.v. irinotecan 10 mg/m²/day on days 1-5 and days 8-12 in 3-week cycles. The temozolomide starting dosage was increased to 125 mg/m²/day at cycle 2 in the absence of grade 3 toxicity or higher. Patients continued study treatment for up to 1 year or until disease progression, unacceptable toxicity, or unwillingness to continue. After 5 cycles of treatment, patients who had not progressed may have received irinotecan once weekly at 125 mg/m² on days 1 and 8.

Assessments

Response was assessed by MRI according to World Health Organization guidelines.³² Mandatory was MRI with at least 1 scan including T1 (with and without contrast), T2, and fluid-attenuated inversion recovery sequences. Response was first assessed at the end of cycle 2. An objective tumor response during the first 4 cycles of treatment was confirmed by a response assessment obtained ≥ 4 weeks after the initial documentation. Continuing response/stable disease (SD) was confirmed every 2 cycles (6 wk) until disease progression or study discontinuation. Clinical benefit was measured as a post hoc assessment and was defined as the proportion of patients with a confirmed objective response and those who had SD for >4 cycles.

Patients were followed for survival for up to 1 year after the last dose of study treatment or discontinuation from the study. For objective tumor response, clinical benefit, TTP, and TTF, patients were censored if they did not have objective or clinical evidence of progressive disease, were removed from the study, or had additional antitumor therapy, including radiation therapy and surgery given as adjuvant therapy and chemotherapy regimens not under study. Safety was evaluated and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. AEs were recorded at study visits and for at least 28 days after the last dose of study treatment.

Statistical Analysis

The study had 80% power to differentiate between an undesirable response rate of 30% and a desirable response rate of 50%. As part of the 2-stage Optimum Simon design,³⁰ an interim analysis for futility was performed at the end of stage 1. Only if at least 6 responses were confirmed in the first 15 evaluable patients enrolled in stage 1 were an additional 31 evaluable patients to be enrolled in the second stage for a total of 46 evaluable patients; 19 confirmed responses was considered a success.

In the primary efficacy analysis, the ERRC disease assessment review determined the objective tumor responses of all patients; these were used as the primary assessment in the objective response analysis. The investigators' response assessments were also collected and were used as secondary assessments in the objective response analyses.

Safety was analyzed in the safety population comprising all enrolled patients who were administered at least 1 dose of study medication.

The primary efficacy endpoint was evaluated in the primary evaluable population (deemed evaluable by the ERRC) comprising the first 46 evaluable patients (predetermined by the 2-stage Optimum Simon design) who formed a subset of the safety population. Patients were counted into the primary evaluable population consecutively based on the date of first treatment with study medication.

Secondary efficacy endpoint analyses were performed in both the primary evaluable population and the local

evaluable population, which comprised those patients from the safety population with measurable disease and at least 1 tumor assessment (both by the investigator) who had completed at least 2 cycles of study treatment or who had progressed.

TTF, TTP, and OS were described using the Kaplan–Meier imputation method; median times and 95% confidence intervals (CIs) were calculated.

Results

Patients

Sixty-six patients were enrolled between April 2007 and April 2010. Patient baseline demographics and disease characteristics are shown in Table 1. Most patients were heavily pretreated or had refractory disease while on chemotherapy; 51 were treated at first relapse and 15 at second or further relapse. The majority of patients were male (68.2%), and the median age was 10.5 years (range, 2–17 y). Most patients had classical medulloblastoma (84.9%), 9 patients (13.6%) had desmoplastic disease, and 1 had an anaplastic variant of

Table 1. Patient and disease characteristics at baseline in the safety population

Characteristics	Patients, n (%)
Sex, n (%)	
Male	45 (68.2)
Female	21 (31.8)
Age, y, median (range)	10.5 (2–17)
Performance status, n (%)	
ECOG or equivalent Lansky–Play scale, n (%)	
0 or 100–90%	39 (59.1)
1 or 80–70%	27 (40.9)
Any signs and symptoms, n (%)	54 (81.8)
Histological classification, n (%)	
Classical	56 (84.9)
Desmoplastic	9 (13.6)
Anaplastic large cell variant	1 (1.5)
No medulloblastoma	1 (1.5)
Disease site, n (%)	
Brain	53 (80.2)
Spinal cord	12 (18.2)
Other	1 (1.5)
No lesion reported	1 (1.5) ^a
Prior treatment, n (%)	
Any chemotherapy	66 (100)
High-dose chemotherapy	14 (21.2)
Radiation therapy	61 (92.4) ^b
Craniospinal irradiation	59 (89.4)
Surgery	66 (100)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

^aNo target lesion at baseline was recorded on the case report form by the investigator and confirmed by central review.

^bFive patients had not received radiation therapy at the time of study entry; all 5 were progressive under sandwich chemotherapy.

medulloblastoma. The target lesions were most commonly in the brain (80.3%).

Patient disposition and study analysis populations are shown in Table 2. Two patients were excluded from the local evaluable population for efficacy as having only nonmeasurable disease, and 1 patient with presumed relapse was subsequently considered to have had radiological changes following re-review by the site 2 years after study entry. The local evaluable population therefore comprised 63 patients. The primary evaluable population comprised the first 46 evaluable patients (by the ERRC)—in total, 48 patients were considered evaluable by ERRC. Eighteen patients were considered not evaluable for the primary efficacy endpoint for reasons including no evaluable assessments after baseline or quality issues concerning radiological images ($n = 7$), no measurable disease (ie, < 10 mm; $n = 5$), no evaluable scan at baseline ($n = 4$), or a combination of these issues ($n = 2$). In addition, 1 patient, finally considered to have radiological changes following review by the site, was removed from the primary efficacy analysis.

Most patients (53%) discontinued treatment due to disease progression or relapse; only 2 patients (3%) discontinued due to treatment-related AEs (Table 2).

Efficacy

Following ERRC assessment, 7 confirmed responses were observed in the first 4 cycles in the first 15 evaluable

Table 2. Patient disposition and study analysis populations

	Number of patients (%)
Study analysis populations	
Safety analysis population	66
Local evaluable population	63 ^a
Primary evaluable population	46
Patient disposition at the end of treatment	
Treated patients	66 (100)
Discontinued due to	
Disease progression or relapse	35 (53.0)
Completed treatment during 1 year	9 (13.6)
Patient refused to continue treatment unrelated to adverse events	4 (6.1)
Adverse events	2 (3.0)
Protocol violation	1 (1.5)
Patient died	0
Other ^b	15 (22.7)

^aOne patient with presumed relapse was now considered to have had radiological changes following re-review by the site 2 years after study entry.

^bOther reasons included: 11 patients on investigator's/physician's decision (6 due to no further benefit gained, 4 no reason given, and 1 had clinical progression); 1 patient had completed 1 y of treatment (not allowed to follow by protocol); investigator error (treatment stopped 1 cycle early); 1 patient following good response proceeded to high-dose chemotherapy; 1 patient proceeded to surgery following a re-scan; 1 patient had difficulty swallowing medication.

patients, allowing for continued enrollment. In the primary evaluable population, there were 15 confirmed objective responses (2 complete responses [CRs] and 13 partial responses [PRs]; Table 3) with an objective response rate of 32.6% (95% CI, 19.5%–48.0%). The study did not meet the primary endpoint of 19 confirmed responses as planned in the protocol. However, 2 other PRs were observed and confirmed at 23 and 27 days but not after ≥ 30 days; in addition to another PR that was observed after the 4th course, these PRs were not considered.

Efficacy endpoints in the local evaluable population are presented in Table 3. The objective response rate in the local evaluable population was 33.3% (1 CR and 20 PRs) during the first 4 cycles. In addition, 2 patients had PRs reassessed 21 and 23 days after the initial PR assessment, thus too early to be considered as confirmed PRs; they were considered per definition as unconfirmed PRs. In the 46 patients of the primary evaluable population, there was a 35% discordance between the results of the ERRC and the local assessments; 4 PRs were reviewed as SDs and 6 SDs were reviewed as PRs. One patient

Table 3. Summary of the efficacy endpoint analyses

	Study Population, n (%)	
	Evaluated by ERRC ($n = 46$)	Evaluated by Local Investigator ($n = 63$)
Objective response ^a , n (%)		
CR	2 (4.3)	1 (1.6)
PR	13 (28.3)	20 (31.7)
SD	19 (41.3)	26 (41.3)
Progressive disease	12 (26.1)	15 (23.8)
Indeterminate	0	1 (1.6)
Objective response rate ^a , n (%)	15 (32.6)	21 (33.3)
95% CI	19.5–48.0	22.0–46.3
Duration of response ^a		
Median, wk	27.0	19.1
Range	7.7–44.1	6.9–46.6
TTP parameter		
Event free at 6 mo, ^b %	46.2	49.6
95% CI	31.3–61.0	36.7–62.6
Median TTP, mo	4.3	5.6
95% CI	2.7–6.4	3.8–7.4
TTF parameter		
Event free at 6 mo, ^b %	37.0	34.9
95% CI	23.0–50.9	23.1–46.7
Median TTF, mo	3.4	3.8
95% CI	2.6–6.1	2.9–5.4

Abbreviations: TTP, time to tumor progression; TTF, time to treatment failure.

^aResponses during the first 4 treatment cycles; in addition, 2 patients had PRs confirmed 21 and 23 days after the initial assessment, thus were considered per definition as unconfirmed PRs.

^bFor both TTP and TTF, probability of being event free at 6 mo was calculated using Kaplan–Meier imputation method.

was considered as having a late response (1 CR after 4 cycles of treatment) by ERRC and local review.

For patients who responded within the first 4 cycles in the primary evaluable population, the median duration of response was 27.0 weeks (7.7–44.1 wk) and in the local evaluable population 19.1 weeks (6.9–46.6). At any time on treatment the median duration of response was 24.1 (7.7–44.1) and 22.4 (6.9–46.6) weeks in these populations, respectively. Of note, 5 patients had prolonged responses, with durations ranging from 30 to 75 weeks, and were treated with adjuvant, consolidation, or maintenance therapy following administration of TEMIRI. Of these patients, 1 had a confirmed PR (total duration 30.1 wk) followed by radiation therapy; 1 had a confirmed CR (total duration 46.6 wk) followed by surgery; 1 had an unconfirmed PR (confirmed 21 days after initial assessment, total duration 57.7 wk) followed by surgery and radiation therapy; 1 had a PR followed by a CR on treatment (total duration 68.9 wk) and had additional chemotherapy other than irinotecan or temozolomide (busulfan and thiotepea at 6 mo after TEMIRI, and cyclophosphamide and valproic acid 6 mo later); and 1 patient had a PR (total duration 75.0 wk) and additional chemotherapy other than irinotecan or temozolomide (etoposide, thiotepea, vincristine, and methotrexate ~4 mo after TEMIRI).

Clinical benefit was observed in 60.9% (95% CI, 45.4%–74.9%) of patients in the primary evaluable population and 68.3% (95% CI, 55.3%–79.4%) of patients in the local evaluable population. The estimated probability of remaining progression free at 6 months was 46.2% (95% CI, 31.3%–61.0%) in the primary evaluable population, and median TTP was 4.3 months (95% CI, 2.7–6.4). Similar results were observed in the local evaluable population (49.6% [95% CI, 36.7–62.6]; median TTP, 5.6 mo [95% CI, 3.8–7.4]).

In the 65 patients who received at least 1 dose of study medication and who had the disease under study, the median survival was 16.7 months (95% CI, 13.3%–19.8%; $n = 65$). During the follow-up period, 43 patients (65.2%) received additional chemotherapy, 14 (21.2%) had reirradiation, and 5 (7.6%) had surgery.

Exposure and Safety

The median number of cycles started was 6 (range, 1–18; Table 4). Forty-six patients (69.7%) had at least 1 cycle

Table 4. Summary of study treatment exposure

	<i>n = 66</i>
Median number of cycles started (range)	6.0 (1–18)
Patients with ≥ 1 cycle delay, <i>n</i> (%)	46 (69.7)
Patients with > 1 cycle delay, <i>n</i> (%)	27 (40.9)
Patients with ≥ 1 irinotecan dose delay, <i>n</i> (%)	10 (15.2)
Patients with ≥ 1 temozolomide dose delay, <i>n</i> (%)	3 (4.5)
Median (range) relative dose intensity for irinotecan	100 (20–550)
Median (range) relative dose intensity for temozolomide	105 (25–173)

delay, and 27 patients (40.9%) had 2 or more delays (median delay, 7 d; range, 1–31 d). Ten patients (15.2%) had at least 1 irinotecan dose delay, and 3 (4.5%) had at least 1 temozolomide dose delay. Of 34 patients reporting any interruption or reduction of study treatment, 19 had hematologic toxicities, 5 had gastrointestinal toxicities, and 6 had other toxicities. Median relative dose intensities were 100% and 105% for irinotecan and temozolomide, respectively.

Across the study period, 60 patients (90.9%) experienced 327 AEs considered possibly related to treatment (Table 5). The most frequently reported AEs of any grade were gastrointestinal disorders, including diarrhea (59.1%), vomiting (56.1%), and nausea (28.8%). Grade 3 gastrointestinal disorders included diarrhea in 5 patients (7.6%) and vomiting and abdominal pain in 1 patient each (1.5%). Grade 3/4 treatment-related hematologic disorders included neutropenia in 11 patients (16.7%), thrombocytopenia in 8 patients (12.1%), and anemia and lymphopenia each in 6 patients (9.1%). Of 65 patients evaluable for laboratory abnormalities, 3 patients (4.6%) experienced grade 3 hypokalemia, and 2 patients (3.1%) each experienced grade 3/4 alanine aminotransferase abnormalities or hyponatremia. Less common grade 3 treatment-related AEs, present only once, were weight loss, hypotension, dehydration, infection, gastroenteritis, hypophosphatemia, and aspartate aminotransferase level increase. No other grade 4 treatment-related AEs were encountered.

Two patients permanently discontinued therapy due to AEs other than disease progression. One patient withdrew due to diarrhea and vomiting (considered treatment related), and 1 patient withdrew due to serious depression (considered unrelated). Seven patients (10.6%) died within 28 days of the last administration of study treatment due to disease progression.

Discussion

This phase II study in heavily pretreated patients is the largest of its kind in pediatric recurrent/refractory medulloblastoma and reported a promising response rate (reviewed by ERRC) of 32.6% after the first 4 cycles of treatment with TEMIRI. The median duration of response was 27 weeks (range, 7.7–44.1 wk). Response rates after 4 cycles of treatment, and the best overall response calculated using local investigator assessments, were similar to those reported by the ERRC. Response was assessed within the first 4 cycles (rather than at any time during treatment) to allow an assessment of TEMIRI to elicit responses earlier than later.

The stringent 2-stage Optimal Simon design was adopted to detect a response rate above 40%, which was not met; nevertheless, the response rate of 32.6% compares favorably with most of those previously reported in patients receiving chemotherapy in this setting.^{6,7,9,10,12–14,17,19} Indeed, we are unaware of any similar response rate reported in a multicenter centrally reviewed study of heavily pretreated patients with recurrent/refractory medulloblastoma. Moreover, clinical

Table 5. Most frequent treatment-related AEs present in >10% of patients in the safety population (n = 66)

Preferred Term	Number of Patients (%)				
	Grade 1	Grade 2	Grade 3	Grade 4	Total
Any AE	10 (15.2)	20 (30.3)	23 (34.8)	7 (10.6)	60 (90.9)
Nonhematologic					
Diarrhea	24 (36.4)	10 (15.2)	5 (7.6)	0	39 (59.1)
Vomiting	27 (40.9)	9 (13.6)	1 (1.5)	0	37 (56.1)
Nausea	15 (22.7)	4 (6.1)	0	0	19 (28.8)
Abdominal pain	10 (15.2)	6 (9.1)	1 (1.5)	0	17 (25.8)
Fatigue	10 (15.2)	2 (3.0)	0	0	12 (18.2)
Decreased appetite	7 (10.6)	4 (6.1)	0	0	11 (16.7)
Constipation	3 (4.5)	4 (6.1)	0	0	7 (10.6)
Hematologic					
Thrombocytopenia	3 (4.55)	6 (9.1)	6 (9.1)	2 (3.0)	17 (25.8)
Neutropenia	-	4 (6.1)	7 (10.6)	4 (6.1)	15 (22.7)
Lymphopenia	1 (1.5)	3 (4.5)	3 (4.5)	3 (4.5)	10 (15.2)
Anemia	1 (1.5)	2 (3.0)	6 (9.1)	0	9 (13.6)

Abbreviation: AE, adverse effect.

benefit was received in 60.9% of the primary evaluable population and 68.3% of the local evaluable population. Approximately 50% of patients completed at least 6 cycles of treatment.

In this analysis, duration of response was censored at the initiation of any new antitumor therapy, including radiation or surgery, to capture the direct benefit of TEMIRI. Of note, however, there were 5 patients who had prolonged responses, with durations ranging from 30 to 75 weeks, who were treated with adjuvant radiation therapy, surgery, or consolidation or maintenance chemotherapy following administration of TEMIRI.

Taking into account the published data, it appears that the TEMIRI regimen leads to an improvement in the objective response rate compared with that reported when irinotecan (16% and 17%)^{9,19} and temozolomide (14% and 16%)^{10,15} were administered as single agents. Disease control also appeared to be improved in this comparison.

Allowing for censoring of patients receiving other antitumor therapy after receiving TEMIRI, 46.2% of patients in the primary evaluable population were progression free at 6 months, and the median TTP was 4.3 months. Survival at 6 months was 79.7%, and median survival was 16.7 months. While many studies in this setting have not reported patient survival data, these current findings (where comparable) are favorable compared with many of those that have.^{12,14,33} In a large study of pretreated, relapsed medulloblastoma from the Children's Cancer and Leukemia Group,³³ 40 patients received cyclophosphamide together with surgery or local radiotherapy, and 22 of these went on to be treated with a high-dose chemotherapy-based strategy. With a median follow-up of 7.4 years, the median survival in these 40 patients was 1.4 years and median event-free survival was 1 year.³³

The combination of irinotecan with standard temozolomide was generally well tolerated and consistent with

exposure to these agents in the pediatric setting or with the disease under study.^{12,17,28,29,34} Indeed, TEMIRI was better tolerated than many high-dose chemotherapy regimens in this setting, which are more intensive without being as effective.

Areas of controversy remain in medulloblastoma research, such as inclusion/exclusion criteria in clinical trials. Indeed, classical WHO criteria mandate bidimensionally measurable lesions with at least 1 diameter >10 mm on an MRI scan. This is not always appropriate in medulloblastoma with frequent thin leptomeningeal disease. However, to measure tumor response of small lesions also remains an issue. Thus, new consensual criteria for inclusion and evaluation of early drug development studies in medulloblastoma are needed.

In summary, in this phase II study in pediatric patients with recurrent or refractory medulloblastoma, although the TEMIRI regimen did not meet the primary efficacy endpoint, it was well tolerated. Newly designed trials are needed that investigate this tolerable combination as a chemotherapy backbone in combination with molecularly targeted drugs. These could include agents targeted to platelet derived growth factor receptor (one of the factors implicated in driving metastasis), sonic hedgehog, or, in particular, poly (ADP-ribose) polymerase 1 inhibitors.³⁵⁻³⁹

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