Prolonged schedule of temozolomide (Temodal) plus liposomal doxorubicin (Caelyx) in advanced solid cancers

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Temozolomide (Temodal) is an oral imidazotetrazine. Increased temozolomide exposure and subsequent depletion of O^6-alkylguanine alkyltransferase may improve the activity of temozolomide. The rationale for investigating temozolomide plus Caelyx is based on their antitumor activity, their formulation and no significant overlapping toxicities. We conducted a study of a prolonged schedule of temozolomide (orally on days 1–7 and 15–21) plus Caelyx (day 1) every 28 days. Twenty-one patients (melanoma $n=10$, sarcoma $n=7$ and other $n=4$) were assigned to four dose levels (DL; temozolomide + Caelyx, mg/m^2): DL1: 100 + 30 ($n=3$ patients), DL2: 100 + 40 ($n=6$ patients), DL3: 125 + 40 ($n=6$ patients) and DL4: 150 + 40 ($n=6$ patients). Dose-limiting toxicities were noted after 2 or more cycles in one patient at DL3 (stomatitis) and one patient at DL4 (grade 4 ANC $\geq$ 7 days). Treatment delays and/or dose reductions (due to hematological toxicity) were necessary in five of six patients receiving DL4 compared with one of six patients at DL3, and one patient at DL1 and 2. Thus, the recommended dose was temozolomide 125 mg/m^2 (daily for 7 days every other week) plus Caelyx 40 mg/m^2 (day 1 every 4 weeks). Other toxicities were mild. Antitumor activity was observed in eight patients, including one complete response (melanoma), three partial responses (one melanoma, two sarcomas) and four patients with stable disease (three melanomas, one Ewing), with a duration lasting from 14 to 135+ weeks. Two melanoma patients showed tumor stabilization in non-irradiated cerebral lesions. This schedule of temozolomide allowed higher dose intensity (1750 mg/m^2 in 4 weeks) compared to the standard 5-day regimen (1000 mg/m^2 in the same amount of time).

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Introduction

Temozolomide (Temodal) is an oral imidazotetrazine that is spontaneously cleaved *in vivo* to monoethyl triazenoimidazole carboxamide (MTIC), a reactive DNA methylating species, forming O^6-alkylguanine as a major cytotoxic lesion. Temozolomide (200 mg/m^2 daily $\times$ 5 every 4 weeks) has reported activity in glioma, melanoma and brain metastases of non-small cell lung cancers [1–3]. The antitumor activity of temozolomide is schedule dependent. Thus, increased drug exposure and subsequent depletion of the DNA repair enzyme O^6-alkylguanine alkyltransferase may improve the antitumor activity of temozolomide [4].

Liposomal doxorubicin (Caelyx; Doxil) is doxorubicin encapsulated in a pegylated liposome with a unique pharmacokinetic profile that results in prolonged circulation time and preservation of the drug in the liposome until it reaches and concentrates in the tumor [5]. This formulation also has a moderate myelotoxicity, stomatitis, alopecia and palmar–plantar erythrodysesthesia, and has demonstrated activity in the treatment of ovarian and breast cancers [6,7]. The rationale for using temozolomide plus liposomal doxorubicin arises from their activity against different tumor types, their formulation permitting long-term exposure to the drugs, as well as their lack of significant overlapping toxicities.

Materials and methods

We conducted a phase I study in order to determine the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of a prolonged schedule of temozolomide combined with liposomal doxorubicin. DLT was defined by the presence of any of the following (NCI-CTC, version 2 grading): neutropenia, grade 4 for 7 days or more; febrile neutropenia; thrombocytopenia, grade 4 or grade 3 for more than 7 days; non-hematologic toxicity, any grade 3 severity (except for vomiting controlled by antiemetics and alopecia); and treatment delays for 2 or more weeks because of toxicity (absence of normal hematological counts or no recovery to grade 1 or less non-hematological toxicity). Secondary objectives included determination of a recommended phase II dosing schedule and description of any antitumor activity (Recist criteria).

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The study population included adult patients with advanced solid tumors (brain metastases were not excluded), ECOG performance status of 0–2, and adequate haematologic, renal and hepatic function. Prior therapy with chemotherapy, immunotherapy and radiotherapy was allowed without any limitation of the type or the total number of prior regimens. The protocol was approved by the Ethics Committee and all patients provided written informed consent. Temozolomide (doses ranged from 100 to 150 mg/m^2/day) was administered orally on days 1–7 and 15–21 of every 28 days; liposomal doxorubicin (doses 30 or 40 mg/m^2) was administered i.v. (90-min infusion) every 4 weeks. Patients were followed by echocardiography every 3 cycles.

Table 1 Patient characteristics

No. of patients	21
Male/female	12/9
Median age (range)	57 (19–74)
ECOG PS	
0	6
1	12
2	3
Prior therapy	
chemotherapy (CT)	7
radiotherapy (RT)	2
CT + RT	5
immunotherapy (± CT or RT)	5
no prior therapy	4

Table 2 Treatment administration

Temozolomide[a] (mg/m^2/day)	Caelyx[b] (mg/m$_2$)	Patients (*N*)	No of cycles	
			Without dose reduction	With dose reduction
100	30	3	17[c]	0
100	40	6	18[c]	0
125	40	6	18	1
150	40	6	14	12

Median number of cycles per patient: 3 (1–10).
[a]Days 1–7 and 15–21 every 28 days.
[b]Every 28 days.
[c]One patient at each dose level had only treatment delay.

Results

Twenty-one adult patients (12 men and nine women) with solid tumors (melanoma $n = 10$, sarcoma $n = 7$, unknown primary tumors $n = 2$, non-small-cell lung cancer $n = 1$ and adenocarcinoma of the maxillary $n = 1$) entered the study. The patients' characteristics are presented in Table 1. The treatment administration is summarized in Table 2.

DLTs were noted after the first cycle only in one patient at dose level (DL) 2 (stomatitis grade 3), and after 2 or more treatment cycles in one patient at DL3 (stomatitis grade 3) and in one patient at DL4 (grade 4 neutropenia for 7 or more days).

Treatment delays and/or dose reductions were necessary in five of six patients receiving treatment with DL4 compared with one of six patients in the DL3 group, and one patient each in DL1 and 2. The reasons for treatment delays and/or dose reductions were haematologic (six patients), skin rash (one patient) and patient request (one patient). Thus, the MTD for this combination regimen was temozolomide 125 mg/m^2 administered daily for 7 days every other week plus Caelyx 40 mg/m^2 every 4 weeks. Non-hematologic toxicities (mainly grade 1/2) included vomiting (oral 5-HT$_3$ antagonists + once daily dexamethasone 4 mg orally were needed only during the first 2–3 days of treatment with temozolomide), anorexia, fatigue, stomatitis and skin erythema. No clinical cardiotoxicity was observed in seven patients who received 5 or more cycles of treatment (two of them were pretreated with anthracyclines). Antitumor activity was observed in eight patients with various tumor types, including one complete response (melanoma), three partial responses (one melanoma, two sarcomas) and four patients with stable disease (three melanomas, one Ewing sarcoma). The duration of antitumor activity lasted from 14 to 135 + weeks. Antitumor activity was noted in the liver, lung, brain and soft tissue metastases. Two melanoma patients demonstrated stable disease in non-irradiated cerebral lesions. Table 3 summarizes the characteristics of patients with signs of antitumor activity.

Table 3 Antitumor activity

Dose level (TMZ/Caelyx)	Tumor type	Response (duration in weeks)	Response site(s)	Prior chemotherapy
100/30	melanoma	SD (22)	liver, lymph nodes	yes
	Ewing sarcoma	SD (41)	lung, liver	yes
100/40	melanoma	CR (135 +)	liver	no
125/40	melanoma	PR (21)	skin	no
	myofibroblastic sarcoma	PR (14)	soft tissue	no
150/40	Ewing sarcoma	PR (28)[a]	peritoneal lymph nodes, soft tissue	yes
	melanoma	SD (34)	lung, cerebral[b], soft tissue	yes
	melanoma	SD (28)	lung, liver, cerebral[b]	no

SD: stable disease; CR: complete response; PR: partial response; TMZ: temozolomide.
[a]Lost to follow-up after 28 weeks.
[b]No prior radiotherapy to the brain.

Discussion

Caelyx was combined with the approved schedule of temozolomide (daily × 5 every 4 weeks) in a phase I study reported by Volm *et al.* [8]. The regimen was well tolerated and both drugs were successfully escalated to doses considered a MTD in prior single-agent studies (Caelyx 40 mg/m^2 + temozolomide 200 mg/m^2 for 5 days every 4 weeks). The extended schedule of temozolomide used in our study allowed better dose intensity of this agent (1750 mg/m^2 in 4 weeks time) compared to the standard 5-day regimen (1000 mg/m^2). No objective responses were observed in Volm's study (eight melanoma patients were treated). In our study, antitumor activity was observed in melanoma patients (two objective responses and three stable diseases of more than 20 weeks duration) and in two heavily pretreated patients with Ewing sarcomas. The prolonged schedule of temozolomide could explain the antitumor activity seen in our study, but to draw a definite conclusion regarding the antitumor activity of temozolomide, a randomized trial comparing the standard to a prolonged schedule of temozolomide is needed.

To our knowledge, there are two reports showing no or limited antitumor activity of Caelyx in pretreated melanoma patients [9,10], but an additive effect of Caelyx in combination with temozolomide cannot be ruled out. Once again, a randomized study comparing temozolomide to temozolomide plus Caelyx might be of particular interest in sarcoma and melanoma patients, and could document the additive effect, if any, of Caelyx and an extended schedule of temozolomide.

Recently, Docetaxel, another cytotoxic drug with a limited activity in melanoma, was combined with the standard schedule of temozolomide as first-line therapy [11]. Interestingly, in this study, 27% of the patients with metastatic melanoma achieved objective responses.

Other temozolomide combination studies have been performed recently in patients with metastatic melanoma using agents such as thalidomide (response rate 26%) [12–14] and interferon (response rate 20%) [14]. A randomized study comparing an extended schedule of temozolomide alone and in combination with these anticancer agents will be of great interest.

Temozolomide can cross the blood–brain barrier and its concentration in the central nervous system is approximately 30% of its concentration in plasma [15]. Temozolomide showed activity in patients with brain metastases from melanoma [16] and non-small cell lung cancers [3]. Two melanoma patients with systemic disease and no life-threatening brain metastases were treated in our study. Brain radiotherapy was omitted in these patients. These metastases remained stable for more than 6 months and no new lesions appeared. In a retrospective case control study, Paul *et al.* reported less central nervous system relapse in temozolomide-treated patients compared to dacarbazine-treated patients [17].

In conclusion, temozolomide 125 mg/m^2 administered daily for 7 days every other week plus Caelyx 40 mg/m^2 every 4 weeks was well tolerated, while DL4 (temozolomide 150 mg/m^2 + Caelyx 40 mg/m^2) was limited by hematologic toxicity. Antitumor activity was seen specifically in patients with Ewing sarcoma and melanoma. Thus, this combination warrants further clinical development.

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