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ORIGINAL ARTICLE

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Phase II study of temozolomide plus pegylated liposomal doxorubicin in the treatment of brain metastases from solid tumours

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Abstract *Objective*: A combination regimen of temozolomide (TMZ) and pegylated liposomal doxorubicin has been evaluated in the treatment of brain metastases from solid tumours. *Study design:* Nineteen consecutive patients (pts) have been enrolled in a prospective phase II trial and treated with TMZ 200 mg/m^2 (days 1–5) and pegylated liposomal doxorubicin 35 mg/m^2 (day 1) every 28 days. The study was prospectively projected according to the Simon's two-stage optimal design. *Results:* Major toxicities have been grade III neutropenia and thrombocytopenia in one patient (pt) and grade III erythrodisesthesia in two pts. Three pts achieved a complete response (CR) and four a partial response (PR), for an overall response rate of 36.8% (95% CI: 19.1–59.2), which exceeded the target activity in the study design. A significant improvement in quality of life was demonstrated by FACT-G analysis. The median Progression Free Survival (PFS) was 5.5 (95% CI: 2.7–8.2) months while the median Overall Survival (OS) was 10.0 months (95% CI: 6.3–13.7). *Conclusions:* The TMZ/pegylated liposomal doxorubicin regimen was well tolerated with an encouraging activity in brain metastases from solid tumours.

Keywords Brain metastases · Pegylated liposomal doxorubicin · Temozolomide · Quality of life · Phase II study

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Introduction

Brain metastases occur in 20–40% of patients (pts) affected by solid tumours [21, 28]. The optimal therapy of brain metastases is still under investigation. Corticosteroids, radiotherapy, surgical therapy, and radiosurgery all have an established role in the management of brain metastatic disease [3, 17, 26] but all remain strictly palliative approaches. Although chemotherapy has not yet emerged as a standard treatment for pts with brain metastases, the current evidence suggests that cytotoxic drugs may indeed have a role in the treatment of selected pts. Several relatively new anticancer drugs have been developed with pharmacokinetic and bio-distribution properties that allow good accumulation in the brain tissue.

An anticancer drug with a significant accumulation in brain tissue is temozolomide (TMZ), a new orally administered imidazo-tetrazine with a mechanism of action and efficacy similar to dacarbazine (DTIC). It has been already used alone or in combination with radiotherapy in the treatment of primary and secondary brain tumours and is currently used in the therapy of glioblastomas also as single agent [1, 4, 5, 18–20]. It is well tolerated, and is therefore a suitable candidate for combination chemotherapy [8]. A recent study has demonstrated that TMZ adjuvant and concomitant

with radiotherapy improves significantly the survival of pts with glioblastoma [24]. In a phase I pharmacokinetic study of TMZ and cisplatin in pts with advanced solid tumours, this combination showed some activity in non-small cell lung cancer (NSCLC) pts. Moreover, objective responses induced by TMZ have been demonstrated also in breast and colon cancers [1, 6]. The good distribution of TMZ in the brain suggests that this drug may be an attractive agent against secondary brain malignancies.

Pegylated liposomal doxorubicin (doxorubicin HCl liposome injection; Doxil or Caelyx, PLD) is a liposomal formulation of doxorubicin, with a low uptake by the reticulo–endothelial system due to the attachment of polyethylene glycol polymers to a lipid anchor. The PLD has demonstrated to be an effective agent against metastatic breast and ovarian cancer and cutaneous T-cell lymphoma [9–12, 16, 22, 29]. It has been recently demonstrated that PLD can also cross the brain–blood barrier with a consequent accumulation in primary and secondary brain lesions; in ten pts with metastatic brain tumours treated with radiolabeled liposomal doxorubicin concurrent with radiotherapy the accumulation of radiolabeled PLD was 7–13 times higher in the metastatic lesions, compared to the normal brain [14]. In a recent case report it is described a patient (pt) affected by a vulvar adenocarcinoma that has metastasized at multiple sites including also brain; in this pt, PLD therapy resulted in a dramatic regression of metastatic lesions and marked improvement in quality-of-life (QoL) [13].

The TMZ and PLD have been already used in combination in phase I clinical studies in the treatment of advanced solid tumours [2, 27]. We have used the TMZ/PLD combination in the treatment of brain metastases derived from solid tumours in order to evaluate the activity and the toxicity profile of the schedule in a prospectively designed phase II study. Moreover, we have evaluated the impact of such combination on the QoL of the pts enrolled in the study.

Patients and methods

Study design

A phase II study was prospectively projected according to the Simon's two-stage optimal design [23]. The primary endpoint was the objective response rate (CR + PR) at the brain site. According to this design a number (n1) of pts enter the first stage of the trial. The accrual continues to a total of n2 pts only if a specified r1 response rate is achieved in the first series. We have selected as target activity a 10–30% response rate, with a 0.05 α error and a 0.20 β error. In this case the treatment under investigation should be considered non-active if it produced less than two responses out of 10 consecutive pts in the first series and fewer than 5/29 pts in the overall series.

Patient selection

The basic requirement for pt accrual was to be carrier of at least one measurable brain lesion. The minimum size of a target lesion in the brain was 2.0 cm. The pts who had completed Whole Brain Radiotherapy (WBRT) and/or any other kind of therapy at least 8 weeks before study entry (or had refused WBRT) and showed progressive disease (PD) at the brain-site at the time of enrollment were considered eligible. The pts were required to be more than 18-year old, to have a WHO/ECOG performance status of 0–2, without of symptomatic heart disease and with a good heart performance (EF% > 50%) evaluated with cardiac scintigraphy and/or ultrasonography, and not pregnant or nursing. Normal liver and kidney biochemistry (total bilirubin < 1.5 mg/dl, aspartate aminotransferase and alanine aminotransferase < 3 times the normal limit, prothrombin and partial thromboplastin < 1.5 times the normal limit and creatinine < 1.2 mg/dl) and histological diagnosis of a single cancer histotype were also required. No pts with previous malignancies were allowed except for adequately treated in situ carcinoma of the cervix or squamous carcinoma of the skin. All the extra-brain sites of disease should also be considered not progressive by the investigators at the time of enrollment in the study. The study was approved by the Institutional Bioethical Committee and all pts provided written informed consent before the beginning of the treatment.

Treatment and monitoring

The TMZ was administered orally at the dose of 200 mg/m^2 daily for five consecutive days under fasting conditions. The PLD was intravenously administered at the dose of 35 mg/m^2 (infusion time 60 min) at the day 1. The treatment was repeated every 28 days. The pts underwent clinical and biochemical examination before entry into the study and then monthly during the study and follow-up; blood counts were assessed weekly during treatment. Each evaluation included complete physical examination, a routine biochemical profile, the assessment of side effects and the identification of any complications. All adverse events were recorded and graded according to CTC-NCI criteria (Version 2.0). Treatment was continued until disease progression, unacceptable toxicity, pt refusal or for a maximum of eight cycles.

Treatment evaluation

Target lesions were assessed by computed tomography (CT) and/or gadolinium-enhanced magnetic resonance imaging (Gd-MRI). The initial examinations had to be performed within 14 days prior the inclusion in the study. Evaluation of target lesions was performed at every third cycles and, if necessary, based on the clinical

situation, according to the WHO/ECOG [25] as described below.

Complete response (CR): disappearance of all known brain metastases. Partial response (PR): 50% or greater decrease in measurable brain lesions or an objective improvement in evaluable, but non-measurable brain lesions. It is not necessary for every brain lesion to have regressed, but no brain lesion should have progressed. Stable disease (SD): brain lesions unchanged (< 50% decrease or < 25% increase in the size of measurable lesions). PD: progression of some or all brain lesions and/or the appearance of new brain lesions.

Disease staging of extra-brain metastases was performed before the beginning of the treatment and then modulated on the basis of different tumour diagnosis or disease sites. A complete reassessment by appropriate imaging was however required every 6 months in all cases.

In order to assess the effect of treatment on the QoL, pts completed the Functional Assessment of Cancer Therapy-General questionnaire (FACT-G, Version 4) [7]. The FACT-G questionnaire was administered before starting treatment and after 3–6–9 months.

Statistical analysis

The QoL data were analysed by ANOVA test. Survival plots were constructed by the Kaplan Meyer method and survival data were analysed by the GraphPad Instat 3.2 statistic software.

Results

Patient characteristics

According to the study design at least two brain responses out of ten consecutive pts were required in order to proceed to the phase II step. Three pts achieved major responses in the first ten pt cohort. Therefore, the study proceeded to the second step and it was completed when a total of seven responses clearly exceeded the six response target in the global pt series. We have treated 19 consecutive pts with different solid tumours. Eighty-two cycles were performed (range: 1–8 cycles). Thirteen out of 19 pts (68.4%) had multiple brain lesions (cortical and/or subcortical and/or cerebellar) and six (31.5%) had a single brain localization (Table 1).

Table 1 Patient characteristics

	No of patients	Percentage
Sex		
Male	7	36.8
Female	12	63.2
Age		
Median	63	
Range	26–81	
Performance status (ECOG)		
0	7	36.8
1	9	47.4
2	3	15.8
Tumour Type		
Breast cancer	8	42.1
Non-small cell lung cancer	6	31.6
Colo-rectal cancer	3	15.8
Melanoma	1	5.3
Ovarian cancer	1	5.3
Brain metastasis		
Single	6	31.6
Multiple	13	68.4
Other metastatic sites		
Single (three lung, two liver, two bone and one breast)	8	42.1
None	6	31.6
Multiple	5	26.3
Previous treatments		
Systemic treatment	12	63.2
RT (out of brain)	3	15.8
WBRT	13	68.4

RT radiotherapy, *WBRT* whole brain radiation therapy

Activity of TMZ/PLD combination

Three CRs (15.8%) were achieved in pts with metastases from breast cancer and lasted 23+, 5+ and 8 months. All of them progressed after WBRT, while two pts had undergone previous systemic chemotherapy. All the three pts had multiple brain lesions and extra-brain disease at different sites. Four PRs (21.0%) were recorded in two pts affected by colo-rectal and two by breast cancer and lasted 10+, 6, 13+ and 4 months, respectively. All the PRs have been defined on the basis of measurable index brain lesions. Eight out of 19 (42.1%) pts remained in SD up to 9+ months and four (21.0%) pts showed a PD. The overall response rate (CR + PR) obtained on brain metastasis was 36.8% (95% CI: 19.1–59.2), while disease control rate was 78.9% (95% CI: 56.3–91.3) (Table 2). Median Progression free survival (PFS) and median overall survival (OS) were 5.5 (95% CI: 2.7–8.2) and 10.0 (95% CI: 6.3–13.7) months, respectively (Fig. 1a, b).

Table 2 Clinical response

	No of patients	Percentage
Best response		
CR	3	15.8
PR	4	21.0
SD	8	42.1
PD	4	21.0
Overall response (CR + PR)(95% CI)	7	36.8 (19.1–59.2)
Disease Control (CR + PR + SD)(95% CI)	15	78.9(56.3–91.3)

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

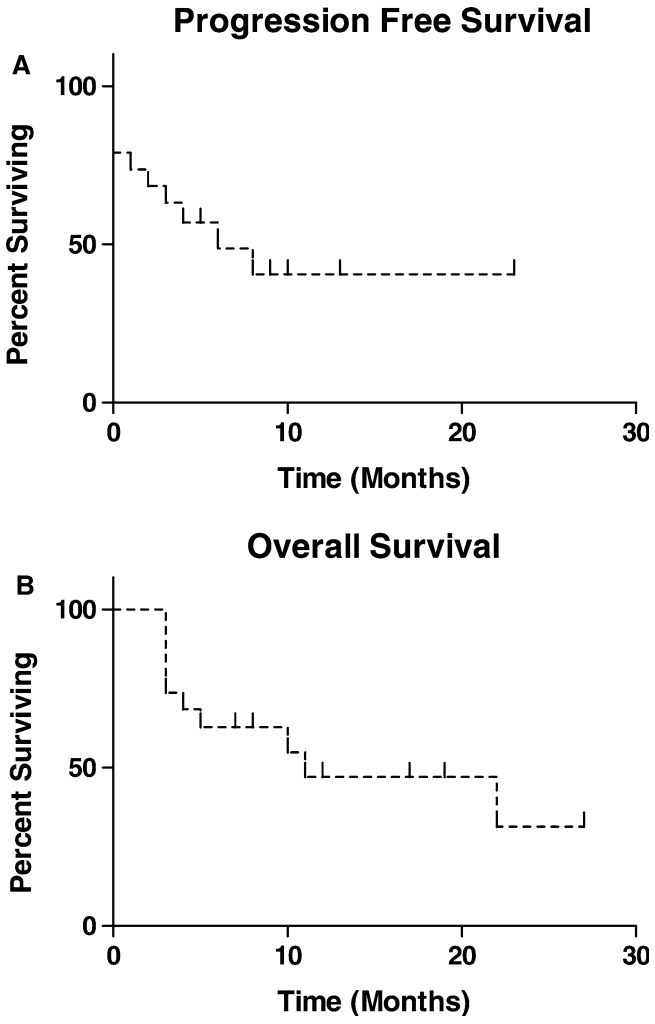

Fig. 1 The PFS and OS have been constructed by the Kaplan–Meyer method. The median PFS was 5.5 months (95% CI: 2.7–8.2) and the median OS was 10.0 months (95% CI: 6.3–13.7)

Toxicity of TMZ/PLD combination

Eighty-two cycles of TMZ/PLD were administered from April 2001 to December 2003. Grade III neutropenia, controlled with the administration of G-CSF and not requiring dose-reduction, and thrombocytopenia were recorded in one pt. Grades II and I (CTC) neutropenia were recorded in other eight and six pts, respectively. Moreover, grades II and I thrombocytopenia developed in five and ten pts, respectively. Grade III erythrodisesthesia occurred in two pts and was controlled with the administration of flavopirimidines and corticosteroids. Grades II and I erythrodisesthesia was also found in four and in six pts, respectively. Grade II nausea/vomiting was recorded in 12 pts and grade II headache in only one pt. Liver or renal or cardiac or severe neurological toxicity were never observed in our series (Table 3).

Effects of TMZ/PLD combination on the QoL

We also measured the quality of life through the questionnaire FACT-G that was well accepted by all the pts. A pt recall is shown in Fig. 2. We observed a highly statistically significant improvement in the QoL as measured by FACT-G, suggesting a clinically relevant impact of combination therapy in pts with brain metastases after 3 and 6 months from beginning of TMZ/PLD treatment ($p \leq 0.0002$ and ≤ 0.0004). The maximal percent increase in mean FACT-G values from baseline occurred after 9 months of therapy (Fig. 2). Matched *t*-test between baseline and 9 months value in pts who where still alive was also significant for FACT-G ($p \leq 0.0001$) indicating that the benefit derived from the treatment was still present after a long-term treatment. The FACT-G improvement involved all the domains and was more pronounced on the Physical and Functional Well Being domains.

Discussion

Radiation therapy is the standard treatment for the majority of pts with brain metastases, while surgical resection should be considered in pts with isolated brain metastasis and no extracranial disease. The role of chemotherapy in the treatment of brain metastases from solid tumours is not clearly defined. However, several relatively new anticancer drugs have been developed

Table 3 Major toxicities (grades I–III according to Common Toxicity Criteria extended by National Cancer Institute, NCI CTC) in the 19 enrolled pts

Toxicity	Grade I		Grade II		Grade III	
	No of pts	Percentage	No of pts	Percentage	No of pts	Percentage
Haemoglobin	12	63.1	3	15.8	0	0
Leucocytes	6	31.6	8	42.2	1	5.2
Platelets	10	52.6	5	26.3	1	5.2
Granulocytes	6	52.6	8	42.2	1	5.2
Nausea	7	36.8	6	31.6	0	0
Vomiting	7	36.8	6	31.6	0	0
Headache	2	10.4	1	5.2	0	0
Erythrodisesthesia	6	31.6	4	21	2	10.4

pts patients

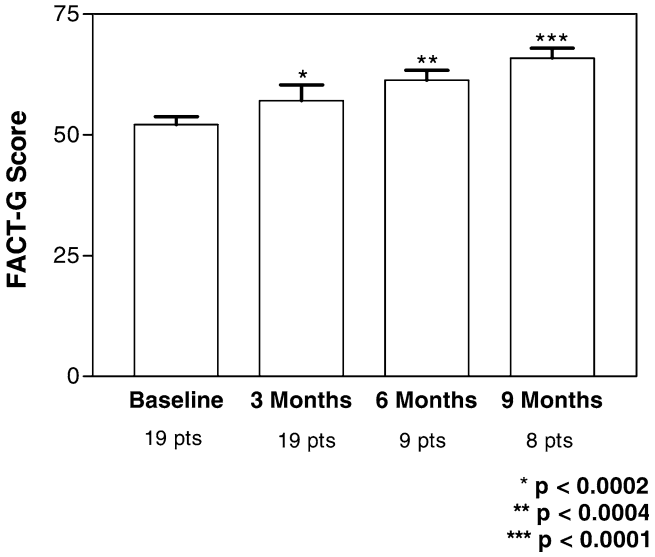

Fig. 2 Variations (mean ± SD) in QoL in TMZ/PLD treated pts. Statistical analysis has been performed by ANOVA comparing different time pts to the baseline values

with pharmacokinetic and bio-distribution properties that allow the selective accumulation in the brain tissue. The TMZ and PLD are two suitable agents for the treatment of brain metastases for their capacity to accumulate in brain tissue and in tumour tissue within brain [8, 15].

In this study, we have evaluated the activity and the toxicity profile of the combination between TMZ and PLD in the treatment of brain metastases derived from several solid tumours in a prospective phase II trial which has been performed according to the two stage optimal design [23]. The recommended phase II dose for this combination, from a previous phase I study, is TMZ 1000 mg/m^2 and PLD 40 mg/m^2 every 4 weeks [27]. We have selected the 35 mg/m^2 PLD dose taking in account that the study accrual might include heavily pretreated pts.

In the present study the overall number of responders to the TMZ/PLD combination exceeded the target, which has been prospectively established and the trial could be therefore defined as positive on the primary outcome of the objective response rate at the brain site. Three CRs (15.8%) were achieved in pts with metastases from breast cancer and four PRs (21.0%) were recorded in two pts affected by colo-rectal and two by breast cancer. Moreover eight (42.1%) pts showed a SD. The overall response rate (CR + PR) of 36.8% (95% CI: 19.1–59.2) obtained on brain metastasis, and the brain disease control rate of 78.9% (95% CI: 56.3–91.3) appears encouraging, although the definition of SD is somewhat difficult in this specific setting. It has to be considered in fact that several pts, who achieved a response after TMZ/PLD treatment, at the time of study accrual were in PD after WBRT

This is the first report, to the best of our knowledge, of the use of TMZ/PLD combination in the treatment of brain metastases even if the two drugs have been already shown to be active as single agents in this setting [1, 4, 5, 15, 18–20]. We have also demonstrated that this combination is able to rescue some of those pts who were refractory to the conventional radiotherapy and to induce in some cases long-lasting responses in a peculiar subset of pts with a bad prognosis where the median OS of 10.0 months can be considered extremely promising.

The majority of the ORs were obtained in pts affected by breast and colo-rectal cancers. While breast tumours are considered highly sensitive to antracyclin-containing regimens, the good activity on colo-rectal cancer suggests a specific sensitivity profile of brain metastasis as compared to other disease sites. This compelling hypothesis needs however to be explored in larger series.

The TMZ/PLD regimen was well-tolerated being scarcely myelotoxic and not inducing mucositis or relevant nausea/vomiting effects. In fact, grade III neutropenia, controlled with the administration of G-CSF and not requiring dose-reduction, and thrombocytopenia were recorded in only one heavily pre-treated pt. Grade III erythrodisesthesia was found in two pts, but it did not require treatment discontinuation and/or dose reduction and was controlled by the administration of flavopirimidines and corticosteroids. The good safety profile of the TMZ/PLD combination has to be considered also taking in account that our pt population has a relatively high mean age (60.8 ± 15 years) and includes also several pts with more than 70 years (6/19 pts). Our findings indicate that the TMZ/PLD combination is well tolerated in elderly pts and can be administered to subjects that could not be treated by conventional approaches both for the presence of brain metastases and old age factors. It has to be considered that an increase in the TMZ dose/intensity should be achieved by a 7 days on, 7 days off schedule at the daily dose of 125 mg/m^2 as recently suggested in a recent phase I study of TMZ/PLD combination [2].

It is now widely accepted that relief from symptoms and protection against brain complications should not be overlooked as therapeutic goals to be achieved in cancer pts with brain metastases. Therefore, the improvement in the QoL may be as important as the increase in survival rates in these pts. We indeed observed a remarkable improvement in the QoL, assessed by FACT-G, during the therapy. It must be noted that the effects of TMZ/PLD combination on QoL persisted after 9 months of therapy. Interestingly, a statistically significant amelioration in the QoL was recorded also in pts who did not achieve an objective response. A suggestive hypothesis is that imaging alone might not fully demonstrate the benefit of chemotherapy on brain metastatic disease.

In conclusions, we have demostrated in a prospectively designed phase II trial that the combination of TMZ and PLD has a definite activity in brain metastases from solid tumours and is a well tolerated treatment also in elder pts. Moreover, the TMZ/PLD combination had a relevant impact on the amelioration of the quality of

life also in pts who did not obtain an OR; an encouraging 10.0 median OS has been also recorded.

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References

1. Abrey LE, Christodoulou C (2001) Temozolomide for treating brain metastases. Semin Oncol 28:34–42
2. Awada A, Gil T, Sales F, Dubuisson M, Verecken P, Klastersky J, Moerman C, de Valeriola D, Piccart MJ (2004) prolonged schedule of temozolomide (Temodal) plus liposomal doxorubicin (Caelyx) in advanced solid cancers. Anticancer Drugs 15:499–502
3. Berk L (1995) An overview of radiotherapy trials for the treatment of brain metastases. Oncology 9:1205–1219
4. Bleehen NM, Newlands ES, Lee SM, Thatcher N, Selby P, Calvert AH, Rustin GJ, Brampton M, Stevens MF (1995) Cancer research campaign phase II trial of temozolomide in metastatic melanoma. J Clin Oncol 13:910–913
5. Bower M, Newlands ES, Bleehen NM, Brada M, Begent RJ, Calvert H, Colquhoun I, Lewis P, Brampton MH (1997) Multicentre CRC phase II trial of temozolomide in recurrent or progressive high-grade glioma. Cancer Chemother Pharmacol 40:484–488
6. Britten CD, Rowinsky EK, Baker SD, Agarwala SS, Eckardt JR, Barrington R, Diab SG, Hammond LA, Johnson T, Villalona-Calero M, Fraass U, Statkevich P, Von Hoff DD, Eckhardt SG (1999) A phase I and pharmacokinetic study of temozolomide and cisplatin in patients with advanced solid malignancies. Clin Cancer Res 5:1629–1637
7. Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, Silberman M, Yellen SB, Winicour P, Brannon J (1993) The functional assessment of cancer therapy scale: development and validation of the general measure. J Clin Oncol 11:570–579
8. Danson SJ, Middleton MR (2001) Temozolomide: a novel oral alkylating agent. Expert Rev Anticancer Ther 1:13–19
9. Dvorak HF, Nagy JA, Dvorak JT, Dvorak AM (1988) Identification and characterization of the blood vessels of solid tumours that are leaky to circulating macromolecules. Am J Pathol 133:95–109
10. Gabizon A, Shmeeda H, Barenholz Y (2003) Pharmacokinetics of pegylated liposomal Doxorubicin: review of animal and human studies. Clin Pharmacokinet 42:419–436
11. Gordon AN, Granai CO, Rose PG, Hainsworth J, Lopez A, Weissman C, Rosales R, Sharpington T (2000) Phase II study of liposomal doxorubicin in platinum- and paclitaxel-refractory epithelial ovarian cancer. J Clin Oncol 18:3093–3100
12. Gordon AN, Fleagle JT, Guthrie D, Parkin DE, Gore ME, Lacave AJ (2001) Recurrent epithelial ovarian carcinoma: a randomized phase III study of pegylated liposomal doxorubicin versus topotecan. J Clin Oncol 19:3312–3322
13. Huang GS, Juretzka M, Ciaravino G, Kohler S, Teng NN (2002) Liposomal doxorubicin for treatment of metastatic chemorefractory vulvar adenocarcinoma. Gynecol Oncol 87:313–318
14. Koukourakis MI, Koukouraki S, Fezoulidis I, Kelekis N, Kyrias G, Archimandritis S, Karkavitsas N (2000) High intratumoural accumulation of stealth liposomal doxorubicin (Caelyx) in glioblastomas and in metastatic brain tumours. Br J Cancer 83:1281–1286
15. Koukourakis MI, Romanidis K, Froudarakis M, Kyrgias G, Koukourakis GV, Retalis G, Bahlitzanakis N (2002) Concurrent administration of Docetaxel and Stealth liposomal doxorubicin with radiotherapy in non-small cell lung cancer: excellent tolerance using subcutaneous amifostine for cytoprotection. Br J Cancer 87:385–392
16. Leighl NB, Burkes RL, Dancey JE, Lopez PG, Higgins BP, David Walde PL, Rudinskas LC, Rahim YH, Rodgers A, Pond GR, Shepherd FA (2003) A phase I study of pegylated liposomal doxorubicin hydrochloride (Caelyx) in combination with cyclophosphamide and vincristine as second-line treatment of patients with small-cell lung cancer. Clin Lung Cancer 5:107–112
17. Mintz AH, Kestle J, Gaspar L, Gaspar L, Hugenholtz H, Fisher B, Duncan G, Skingley P, Foster G, Levine M (1996) A randomized trial to assess the efficacy of surgery in addition to radiotherapy in patients with single cerebral metastasis. Cancer 78:1470–1476
18. Newlands ES, Blackledge GR, Slack JA, Rustin GJ, Smith DB, Stuart NS, Quarterman CP, Hoffman R, Stevens MF, Brampton MH (1992) Phase I trial of temozolomide (CCRG81045: M and B 39831: NSC 362856). Br J Cancer 65:287–291
19. O'Reilly SM, Newlands ES, Glaser MG, Brampton M, Rice-Edwards JM, Illingworth RD, Richards PG, Kennard C, Colquhoun IR, Lewis P (1993) Temozolomide: a new oral cytotoxic chemotherapeutic agent with promising activity against primary brain tumours. Eur J Cancer 29A:940–942
20. Parney IF, Chang SM (2003) Current chemotherapy for glioblastoma. Cancer J 9:149–156
21. Posner JB (1992) Management of brain metastases. Rev Neurol 148:477–487
22. Rivera E, Valero V, Arun B, Royce M, Adinin R, Hoelzer K, Walters R, Wade JL III, Pusztai L, Hortobagyi GN (2003) Phase II study of pegylated liposomal doxorubicin in combination with gemcitabine in patients with metastatic breast cancer. J Clin Oncol 21:249–3254
23. Simon R (1989) Optimal two-stage designs for phase II clinical trials. Control Clin Trials 10:1–10
24. Stupp R, Mason WP, Van Den Bent MJ, Weller M, Fisher B, Taphoorn M, Brandes AA, Cairncross G, Lacombe D, Mirimanoff RO (2004) Concomitant and adjuvant temozolomide (TMZ) and radiotherapy (RT) for newly diagnosed glioblastoma multiforme (GBM). Conclusive results of a randomized phase III trial by the EORTC Brain & RT groups and ncic clinical trial group. Proc Am Soc Clin Oncol 22:(Abst 2)
25. Vantongelen K (eds) (1994) A practical guide to EORTC studies: evaluation, criteria, scoring scales and instruments. EORTC, Brussels
26. Vecht CJ, Haaxma-Reiche H, Noordijk EM, Padberg GW, Voormolen JH, Hoekstra FH, Tans JT, Lambooij N, Metsaars JA, Wattendorff AR (1993) Treatment of single brain metastasis: radiotherapy alone or combined with neurosurgery. Ann Neurol 33:583–590
27. Volm M, Oratz R, Pavlick A (2000) A phase I study of liposomal doxorubicin and temozolomide in patients with advanced cancer. Proc Am Soc Clin Oncol 19:(Abst 872)
28. Walker AE, Robins M, Weinfeld FD (1985) Epidemiology of brain tumours: the national survey of intracranial neoplasms. Neurology 35:219–226
29. Wollina U, Dummer R, Brockmeyer NH, Konrad H, Busch JO, Kaatz M, Knopf B, Koch HJ, Hauschild A (2003) Multicenter study of pegylated liposomal doxorubicin in patients with cutaneous T-cell lymphoma. Cancer 98:993–1001