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Combination raltitrexed (Tomudex®)–oxaliplatin: a step forward in the struggle against mesothelioma? The Institut Gustave Roussy experience with chemotherapy and chemo-immunotherapy in mesothelioma

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Abstract

The aim of this study was to review the experience of the Institut Gustave Roussy in 163 patients with malignant mesothelioma over a 9-year period. Data from seven consecutive prospective trials, four of chemo-immunotherapy and three of chemotherapy were reviewed. The rationale, methods and results of these trials are summarised and discussed. 98 patients were included in four phase II trials of chemo-immunotherapy whose common denominator was a combination of cisplatin and α-interferon. The response rate ranged from 15% to 40%. High-dose weekly cisplatin combined with α-interferon yielded the highest response rate but the toxicity of this regimen was considered unacceptable. Neither higher doses of α-interferon or the addition of mitomycin C or interleukin-2 to the regimen were able to enhance the activity of this combination. 18 patients were included in a paclitaxel–cisplatin phase II trial. The response rate was only 6% (95% confidence interval (CI): 0–24) and toxicity was also significant. This regimen was, therefore, considered ineffective. Of 17 patients with mesothelioma included in a phase I trial that combined raltitrexed and oxaliplatin, 6 (35%) obtained a partial response. Responses were seen even in cisplatin-refractory mesothelioma. Preliminary results of a subsequent ongoing phase II trial using raltitrexed (3 mg/m^2) and oxaliplatin (130 mg/m^2) have confirmed this promising activity with a 30% (9/30) response rate (95% CI: 15–49). The tolerance of this outpatient regimen is acceptable (no significant haematological toxicity and no alopecia) and compares favourably with that of our previous regimens. The final results concerning response and survival are required to confirm the efficacy of this combination. The preliminary results of two studies suggest promising activity with the combination of raltitrexed-oxaliplatin in malignant mesothelioma. The efficacy/toxicity ratio of this combination compares favourably with that of our previous chemotherapy and chemo-immunotherapy regimens.

Keywords: Mesothelioma; Chemotherapy; Immunotherapy; Raltitrexed; Oxaliplatin

1. Introduction

Malignant mesothelioma is an invariably lethal neoplasm, with a median survival of approximately 1 year [1–3]. Although rare, its incidence is on the increase and is expected to continue rising over the coming decades [4]. This increase is attributed to asbestos exposure. The histological diagnosis is notoriously difficult and there is no standard therapy, although surgery, chemotherapy, immunotherapy and phototherapy have been used. Radiation therapy of a short duration delivered to surgical scars after diagnostic procedures has been reported to prevent malignant seeding and is now widely recommended [5]. In multivariate analysis, the main independent adverse prognostic factors include a poor performance status, old age, an advanced stage, a non-epithelial histology and a platelet count $>400\,000/\mu l$ [1,2,6].

The role of chemotherapy in malignant mesothelioma has recently been reviewed extensively [6–9]. Mesothelioma is relatively refractory to chemotherapy and no

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regimen has emerged as a standard for care. Combination chemotherapy has not afforded any clear advantage over single agents but preliminary evidence suggested that dose-escalated chemotherapy (doxorubicin and cisplatin) or new antimetabolites were active [8]. Assessing the role of chemotherapy is usually hampered by many difficulties: small-sized studies, a lack of identification of prognostic parameters, inaccurate staging, variations in response criteria, no confirmation of responses by re-evaluating them at least 4 weeks later, short-lived stabilisation erroneously considered as an index of the activity of chemotherapy (although the indolent evolution of the disease is well-known), and the absence of randomised studies. This is why we decided to summarise our experience with chemotherapy and chemotherapy–immunotherapy prospective trials over a 9-year period at Institut Gustave Roussy in one and the same article.

2. Patients and methods

From 1991 to 1999, seven prospective studies of chemo-immunotherapy or chemotherapy were conducted in patients with mesothelioma at the Institut Gustave Roussy [10–16].

Eligibility criteria included histologically proven mesothelioma of the pleura or the peritoneum, measurable disease on a computed tomography scan, WHO performance status $\leqslant 2$, adequate bone marrow and liver functions, age $\leqslant 18$ years and written informed consent.

Slides were reviewed both by a pathologist from the Institut Gustave Roussy and a pathologist from the French Mesothelioma Registry Panel of Pathologists.

Radiotherapy, delivered to biopsy tracts, was usually given to prevent local involvement by mesothelioma before inclusion. Patients were not to have received previous chemotherapy, except in the last two raltitrexed-oxaliplatin studies.

Target lesions included bidimensionally measurable masses or unidimensionally measurable thickening of the pleura or peritoneum $\geqslant 1$ cm seen in at least two contiguous sections on computer tomography (CT) scan. The overall tumour target volume was calculated as the sum of all target lesions. Complete response was defined as the disappearance of all measurable lesions. Partial response was defined as a reduction of greater than 50% compared with pretreatment values, for at least a month. Responses had to be confirmed after at least 4 weeks. Stable disease was defined as $<50\%$ reduction and a $<25\%$ increase in target lesions, lasting for at least 12 weeks. All responses were reviewed blindly by at least two independent observers including at least one radiologist. Since 1997, responses have always been reviewed by an expert independent external radiologist.

3. Results

3.1. Chemo-immunotherapy trials

Four prospective trials of chemo-immunotherapy were conducted from 1991 to 1997, of which one was a phase I–II trial and three were phase II trials (Table 1). Their common denominator was a combination of cisplatin and α-interferon. The rationale for designing this series of trials was based on the following: (i) cisplatin is recognised as one of the most active drugs in mesothelioma although this neoplasm is considered poorly chemo-sensitive [17]; (ii) the dose intensity of cisplatin has been suggested to be determinant in treatment outcome in various neoplasms [18,19]; indeed promising results have been reported with very high-dose [20] or weekly cisplatin [21] in short series; and a marked increase in cisplatin cytotoxicity was demonstrated when α-interferon was added in mesothelioma xenografts [22].

3.1.1. Phase I–II study of weekly cisplatin and α-interferon [10]

From 1991 to 1992, 26 patients were assigned to receive a combination of weekly cisplatin 60 mg/m^2 and α-interferon given subcutaneously at 3×10^6 IU, each dose being administered every day for 4 consecutive days a week. Therapy was given as a 5-weeks on/3 weeks off schedule or a 4 weeks on/4 weeks off schedule.

Toxicity was significant and included grade 3–4 haematological toxicity (30%), vomiting (40%), peripheral neurotoxicity (8%) and severe asthenia with a decrease in the performance status (56%). However, a promising 40% (95% (confidence interval) CI: 20–60) response rate was obtained, mostly in patients with epithelial mesothelioma and the median duration of response was 11 months (range: 5–32).

These encouraging results prompted us to explore the chemo-immunotherapy strategy further.

3.1.2. Phase II study of cisplatin and high-dose α-interferon [11]

The next step consisted of testing higher doses of α-interferon with the same cisplatin schedule. From 1993 to 1994, 30 patients were given the previous schedule with α-interferon (6×10^6 IU).

This regimen was associated with unacceptably high toxicity, including severe asthenia (100%), renal failure (3%), grade 3–4 haematological toxicity (30%), grade 3–4 vomiting (53%) and grade 3 neurotoxicity (13%). Moreover, the response rate was only 27% (95% CI 13–46) which compared unfavourably with that of our previous trial.

3.1.3. Phase II study of cisplatin, α-interferon and mitomycin C [12]

Mitomycin C was added to the regimen with the goal of increasing its efficacy. This decision was based on

preclinical and clinical data that suggested significant activity of mitomycin C in mesothelioma [23]. The schedule was simplified and the cisplatin doses were reduced to improve the patients' quality of life. This regimen consisted of cisplatin 75 mg/m^2 on day 2, α-interferon (3×10^6 IU/day) from day 1 to day 4 and mitomycin C (10 mg/m^2 on day 2). Cycles were repeated every 4 weeks and 24 patients were treated with this schedule from 1995 to 1996.

As expected, toxicity was lower than that observed in our two previous trials and included mainly severe asthenia (17%), neurological toxicity (17%), grade 3–4 vomiting (21%), thrombocytopenia (17%) and neutropenia (8%). However, the activity was limited with a response rate of only 21% and time to progression of only 6 months (Table 1).

3.1.4. Phase II study of cisplatin, α-interferon and interleukin-2 [13]

Intrapleural interleukin-2 was demonstrated to yield some activity in low-stage mesothelioma [24] and promising results were reported with combination cisplatin-α-interferon and intravenous high-dose interleukin-2 in melanoma [25]. However, the severe toxicities associated with this schedule have been underscored. Based on our previous experience of high toxicity associated with chemo-immunotherapy in a few selected mesothelioma patients, we did not feel that such a regimen would be feasible in this population. This is why we chose to treat our patients with lower doses of interleukin-2 using the subcutaneous (s.c.) versus the intravenous route, as we had done in renal cancer [26]. According to Gehan's model, at least 14 patients were required to exclude the hypothesis of a response rate exceeding 20%, with a β risk of 0.05.

From August 1996 to September 1997, 18 patients entered this phase II study. The regimen was a combination of cisplatin (100 mg/m^2 on day 1), s.c. α-interferon (3×10^6 IU given three times per week, every week), and s.c. interleukin-2 (9×10^6 IU over 5 days per week, for 2 weeks). Cycles were to be administered every 3 weeks, tolerance permitting. Tumour assessment was performed after two cycles. Responders were to receive two further cycles, repeated every 4 weeks.

Tolerance was particularly poor in this trial, with 3 of 18 patients (17%) being withdrawn from the study prematurely due to severe toxicity. Toxicity included grade 3–4 vomiting (40%), although 5-HT3 serotonin inhibitors were systematically given as premedication, grade 3-4 neutropenia or thrombocytopenia (33%), grade 2 skin toxicity (7%) and severe asthenia (33%). Only 2 patients obtained a partial response (Table 1) and this

Table 1
Results of 4 trials of chemo-immunotherapy (1991–1997)

	CDDP–α IFN ($n=26$) *n* (%)	CDDP–HD α IFN ($n=30$) *n* (%)	CDDP–α IFN–Mitomycin C ($n=24$) *n* (%)	CDDP–α IFN–IL2 ($n=18$) *n* (%)
Sex: men/women	21 (81)/5 (19)	27 (90)/3 (10)	14 (58)/10 (42)	12 (67)/6 (33)
Median age (range) (years)	58 (31–69)	58 (44–67)	53 (35–71)	56 (43–67)
Asbestos exposure	15 (58)	18 (60)	14 (58)	–
Thrombocytosis (>400 000/μl)	8 (31)	5 (17)	–	–
UICC staging: stage I/II/III/IV	0 (0)/9 (35)/ 12 (46)/2 (8)[a]	0 (0)/14 (47)/ 15 (50)/1 (3)	2 (8)/10 (42)/ 7 (29)/2 (8)[a]	0 (0)/9 (50)/ 5 (28)/4 (22)
Histological subtype:				
Epithelial	14 (54)	17 (57)	18 (75)	17 (94)
Mixed	9 (35)	10 (33)	5 (21)	1 (6)
Fusiform	3 (12)	1 (3)	1 (4)	0
Unknown	0	2 (7)	0	0
Performance status: 0/1/2	5 (19)/14 (54)/7 (27)	–	–	12 (67)/6 (33)/0
Primary site; pleura/peritoneum	23 (88)/3 (12)	30 (100)/0	22 (92)/2 (8)	18 (100)/0
Response[b]				
Complete response	0	1 (3)	0	0
Partial response	10 (40)	7 (23)	5 (21)	2 (15)
Stable disease	4 (16)	13 (43)	10 (42)	9 (69)
Response rate (95% confidence interval)	40% (20–60)	27% (13–46)	21% (3–36)	15% (2–44)
Median time to progression (months) (range)[c]	8	7 (5–12)	6	
Median survival (months) (range)[c]	12 (5–32)	15 (5–32)	12	15
1-year survival	50%	–	50%	57%

HD, high dose; CDDP, cisplatin; α IFN, alpha interferon; IL2, interleukin-2.

[a] For some patients staging was unknown.

[b] $n=25$, 30, 24 & 18, respectively, were evaluable.

[c] Where available.

strategy was considered highly toxic and probably ineffective.

3.2. Chemotherapy trials

3.2.1. Phase II study of cisplatin and paclitaxel [14]

In 1994–1995, promising results were reported with paclitaxel in mesothelioma, both in animal experiments [27,28] and in the clinic [29]. Moreover, synergistic activity of paclitaxel combined with cisplatin was suggested *in vivo* with the nude mouse model developed by Chahinian and colleagues [27].

This was the rationale underlying the phase II study of cisplatin–paclitaxel in unpretreated mesothelioma, conducted from November 1995 to May 1996. Paclitaxel was given first at a dose of 200 mg/m^2 as a 3-hourly infusion, followed by cisplatin at a dose of 100 mg/m^2, one cycle every 3 weeks, according to the schedule developed in our institution in non-small cell lung cancer [30]. The Gehan model was used to calculate the number of patients required concluding that the regimen was efficient if the true response rate was below 20%, with a β risk of 0.05 and a type 1 error of 0.10.

18 patients entered this study (Table 2). Although tolerance was considered acceptable, (28% grade 3–4 neutropenia and 22% grade 1–2 peripheral neurological toxicity), the results were very disappointing with only 1 partial response and a response rate of 6% (95% CI: 0–24). This combination was thus considered ineffective and the trial was stopped early.

3.2.2. Phase I study of raltitrexed and oxaliplatin [15]

Besides chemo-immunotherapy, patients with mesothelioma have routinely been proposed entry into phase I trials since the beginning of the 1990s, so that new drugs and new drug combinations could be screened in the clinic. In 1997, we developed a phase I study that combined raltitrexed (Tomudex®) and oxaliplatin in advanced solid neoplasms [15]. This study was intended to be an alternative to the active 5-fluorouracil (FU)–oxaliplatin regimen, with 5-FU being replaced by raltitrexed, another thymidylate synthase inhibitor that is easier to handle. The study objectives were to determine the recommended doses for subsequent development of this combination, mainly in advanced colorectal cancer. Patients with orphan neoplasms, as well as those with colorectal cancer, were proposed entry into the study. The final results indicated that this outpatient combination was well tolerated with no alopecia and no significant haematological toxicity. The recommended doses in the combination regimen were the same as those used for single-agent schedules: raltitrexed (3 mg/m^2), followed by oxaliplatin (130 mg/m^2) in a 2-h infusion, were repeated every 3 weeks.

The first patient with mesothelioma included in this trial was a 48-year-old man with a bulky mesothelioma

Table 2
Results of three trials of chemotherapy (1997–1999)

	Paclitaxel–CDDP phase II ($n=18$) n (%)	Raltitrexed–oxaliplatin phase I ($n=17$) n (%)	Raltitrexed–oxaliplatin phase II (preliminary results, $n=30$) n (%)
Sex: men/women	15 (83)/3 (17)	13 (76)/4 (24)	23 (77)/7 (23)
Median age (range) (years)	58 (35–70)	55 (29–71)	59 (43–73)
Asbestos exposure	–	8 (47)	17 (57)
Thrombocytosis (>400 000/μl)	–	9 (53)	14 (47)
Histological subtype:			
Epithelial	15 (83)	16 (94)	22 (73)
Mixed	1 (6)	1 (6)	5 (17)
Fusiform	2 (11)	0	0
Unknown	0	0	3 (10)
Performance status: 0/1/2	6 (33)/10 (56)/2 (11)	3 (18)/10 (59)/4 (24)	9 (30)/18 (60)/3 (10)
Primary site: pleura/peritoneum	18 (100)/0	16 (94)/1 (6)	28 (93)/2 (7)
Response:			
Complete response	0	0	0
Partial response	1 (6)	6 (35)	9 (30)
Stable disease	11 (65)	7 (41)	14 (47)
Response rate (95% confidence interval)[a]	6% (0–24)	35% (13–61)	30% (15–49)
Median time to progression (months) (range)[b]	–	8 (2–13)	Too early
Median survival (months) (range)$_b$	12	13 (2–22)	Too early
1-year survival	50%	53%	Too early

[a] $n=17$, 17 and 30, respectively, where evaluable.
[b] Where available.

of the pleura. He suffered from pain, short breath, sweating, fever and weight loss. His performance status was only 2. Biological studies provided evidence of a major inflammatory syndrome and thrombocytosis. He had received the cisplatin–interleukin-2–α-interferon combination a few months earlier and this treatment had been poorly tolerated and inefficient as his disease had progressed under chemotherapy. The patient was thus considered cisplatin-refractory. After a few cycles of raltitrexed–oxaliplatin, he obtained total pain relief, complete resolution of asthenia and dyspnoea and was able to cycle again. His weight increased by 20 kg. The chest CT scan showed a major partial response (Fig. 1). Progressive disease was again detected 10 months after the first cycle and he was challenged again by the raltitrexed–oxaliplatin combination and obtained a minor response with a clinical benefit. He survived 22 months from the beginning of this therapy.

Overall, we included 17 patients with mesothelioma in this phase I study: 6 achieved a partial response (35%), including 4 cisplatin-pretreated patients, whereas 4 other patients had a short-lived response that was not confirmed by a CT scan 4 weeks later. Responses were reviewed by an independent radiologist. The median time to progression was 8 months (2–13) and the median survival was 13 (2–22) and 17 (5–56+) months since inclusion in the study and since diagnosis, respectively (Table 2). A number of patients obtained a clinical benefit. Toxicity was limited and is detailed elsewhere [15]. These results seemed particularly promising, given that 10 of 17 patients had previously received chemotherapy, including 5 who were considered cisplatin-refractory (progression during cisplatin or during the following 6 months).

3.2.3. Phase II study of raltitrexed and oxaliplatin [16]

In April 1998 we initiated a phase II study in mesothelioma based on these encouraging results. Two groups of target patients were defined: chemotherapy-naïve patients and pretreated patients. The number of

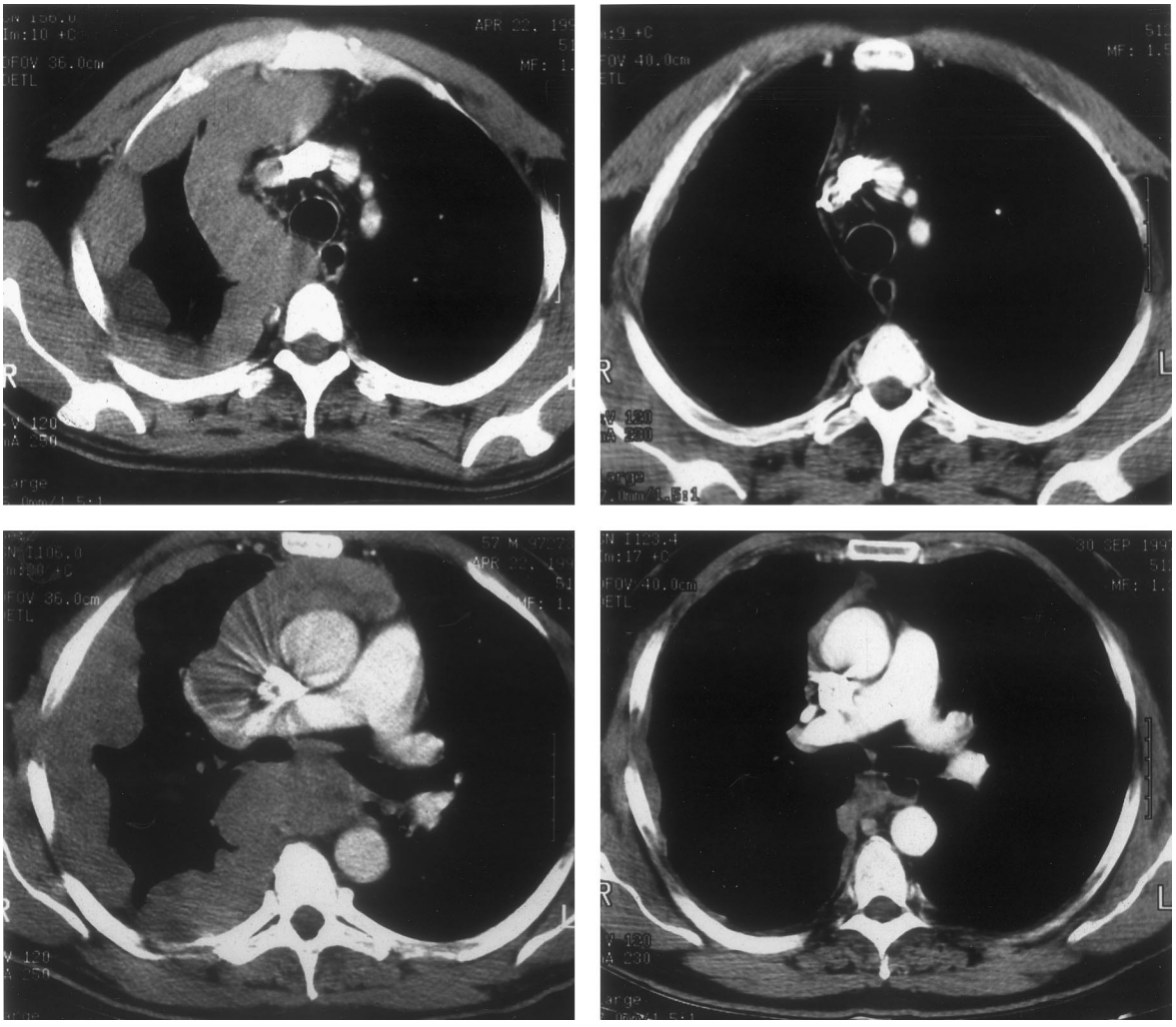

Fig. 1. Chest computed tomography (CT) scan of a patient with malignant mesothelioma before (left) and 3 months after (right) raltitrexed–oxaliplatin combination.

patients in the first group was calculated using the Simon model with a power of 90% to conclude that the regimen is efficient if the true response rate is equal to 30% and with a type 1 error of 10% to conclude that the treatment is efficient if the true response rate is $=10\%$. In the pretreated group, the number of patients was calculated with a power of 90% to conclude that the regimen is efficient if the true response rate is $=20\%$ and with a type 1 error of 10% to conclude that the treatment is efficient if the true response rate is $=5\%$.

The schedule of the regimen is the same as that of the phase I trial: raltitrexed (3 mg/m^2) was given first as a 15-min infusion and followed 45 min later by oxaliplatin (130 mg/m^2) as a 2-h infusion, every 3 weeks in the outpatient clinic. The clinical benefit was assessed using a visual analogue scale for five symptoms, according to a previously recommended methodology [31]. Accrual to this last study was stopped during the summer of 1999. The preliminary results obtained in 30 patients were recently presented [16] and are summarised in Table 2. The excellent tolerance was confirmed and to date, 9 out of 30 patients (30%) have obtained a partial response, including 2 pretreated patients. It is too early to draw conclusions regarding the duration of response, time to progression, the clinical benefit and survival which are awaited at the end of the year 2000.

4. Discussion

The first generation of regimens developed at the IGR in mesothelioma combined cisplatin and cytokines. Although the results of our first trial of weekly cisplatin and α-interferon had shown promising efficacy, albeit with major toxicity [10], we were unable to improve these early results and demonstrate a benefit in combining chemotherapy and immunotherapy in malignant mesothelioma. Neither higher doses of α-interferon nor the addition of mitomycin C or interleukin-2 were able to increase the activity of the cisplatin-α-interferon combination [11–13]. The high response rate obtained in our first cisplatin-α-interferon trial may have been related to the weekly dose-intensive schedule of cisplatin, and not to the adjunction of the cytokine. This argues in favour of shortening the time between chemotherapy cycles ('dose-dense chemotherapy'), an approach reviewed elsewhere [19], to obtain a potential benefit. A 36% response rate has been reported in 14 mesothelioma patients with weekly cisplatin at a dose of 80 mg/m^2, suggesting that resistance to cisplatin could be partially circumvented by dose escalation [21]. The high toxicity of the weekly cisplatin and α-interferon combination however precludes its use in clinical practice or the development of a large phase III study. Various cytokines have been investigated *in vitro* and *in vivo*, and have been tested in clinical trials in mesothelioma [32]. Although encouraging activity was originally suggested by preclinical data [22,33], the use of systemic interferons and/or interleukin-2 as single agents [34–36] or in combination [37–42] produced disappointing results.

With a response rate of only 6% in 18 patients, the cisplatin–paclitaxel regimen was also considered inefficient in mesothelioma. These poor results obtained with a combination regimen confirm the lack of activity of single-agent paclitaxel [43,44].

In spite of the above, our preliminary results with the raltitrexed-oxaliplatin combination look promising in mesothelioma. For the first time in our experience, a regimen seems to yield significant efficacy ($\geqslant 30\%$ response rate in our final phase I and preliminary phase II studies) along with an acceptable tolerance. Haematological toxicity was not marked and there was no alopecia with this combination. Moreover, it was administered as an outpatient infusion and this may improve the patients' quality of life. This regimen was initially tested due to the demonstration *in vitro* of synergy between oxaliplatin and some thymidylate synthase inhibitors. It was subsequently developed in mesothelioma based on impressive results in the first patients treated in our phase I trial [15,16].

How can we explain the activity of the raltitrexed–oxaliplatin combination in mesothelioma? Firstly, the efficacy of antimetabolites has recently been re-assessed in this malignancy and some of them may really be active drugs. Although the activity of single agent 5-FU has not been adequately assessed in this setting by a well-designed trial, Chahinian and Rusch reported a cumulative 20% response rate in older studies [6]. More recently, novel antimetabolites have been investigated in mesothelioma, although the activity of single-agent raltitrexed is unknown. Raltitrexed is a folate-based quinazole-selective, specific thymidylate synthase inhibitor that undergoes extensive intracellular polyglutamation. Polyglutamation prolongs both the intracellular retention of raltitrexed and the inhibition of thymidylate synthase, leading to high levels of cytotoxicity, a property hitherto not observed with non-polyglutamated analogues [45]. High-dose methotrexate and edatrexate, two antifolates were considered promising for the treatment of mesothelioma since they yielded a response rate of 37% and 18–25%, respectively [46–48]. Two other antifolates, trimetrexate and 5,6 dihydro-5′-azacytidine (DHAC), showed no or limited activity [49–51]. Recently, 4 of 7 patients with mesothelioma who received the cisplatin–MTA (multitargeted antifolate) combination obtained a partial response in a phase I trial [52]. MTA is an antimetabolite that acts by inhibiting both thymidylate synthase and dihydrofolate reductase. The activity of single-agent gemcitabine has been variable, ranging from 0 to 31% [53–55] and combining it with cisplatin led to a promising 47.6% response rate in 21 patients entered in a recent phase II trial [56].

Secondly, although the activity of single-agent oxaliplatin is also unknown in mesothelioma, its adjunction to raltitrexed may have increased the activity of the regimen. Preclinical studies have demonstrated that many tumours with either intrinsic or acquired resistance to cisplatin respond to oxaliplatin [57]. The clinical spectrum of activity of these drugs is different [58] and this difference may account for the activity of oxaliplatin in mesothelioma, even though cisplatin is considered only moderately active [6,17]. The absence of cross-resistance between these drugs has been specifically correlated with mismatch repair deficiency [59,60] and this is currently being investigated in mesothelioma in our laboratory.

Thirdly, evidence of a synergistic or an additive effect between oxaliplatin and thymidylate synthase inhibitors has been demonstrated both *in vitro* and *in vivo* [61]. The combination of raltitrexed and oxaliplatin may therefore act synergistically in the clinic and this could explain the high activity of this combination in various neoplasms [15,16,62].

The final results of our raltitrexed–oxaliplatin phase II trial are awaited to confirm whether this combination is truly active or not. The early results obtained recently with new-generation antimetabolites warrant phase III trials. Defining a standard chemotherapy arm in mesothelioma is, however, difficult. An international randomised phase III trial has recently been initiated in mesothelioma patients to compare the cisplatin–MTA combination with cisplatin alone. The European Organization for Research and Treatment of Cancer (EORTC) is also beginning a phase III study comparing the raltitrexed–cisplatin combination with cisplatin. The choice of cisplatin in the combination arm, as opposed to oxaliplatin in these studies is questionable since the latter would have provided a different antitumour effect and it is easier to use, as it avoids hospitalisation. The results of these trials are none the less eagerly awaited.

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