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Trimodality therapy for malignant pleural mesothelioma: results from an EORTC phase II multicentre trial

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ABSTRACT: The European Organisation for Research and Treatment of Cancer (EORTC; protocol 08031) phase II trial investigated the feasibility of trimodality therapy consisting of induction chemotherapy followed by extrapleural pneumonectomy and post-operative radiotherapy in patients with malignant pleural mesothelioma (with a severity of cT3N1M0 or less).

Induction chemotherapy consisted of three courses of cisplatin 75 mg·m^{-2} and pemetrexed 500 mg·m^{-2}. Nonprogressing patients underwent extrapleural pneumonectomy followed by post-operative radiotherapy (54 Gy, 30 fractions). Our primary end-point was ''success of treatment'' and our secondary end-points were toxicity, and overall and progression-free survival.

59 patients were registered, one of whom was ineligible. Subjects' median age was 57 yrs. The subjects' TNM scores were as follows: cT1, T2 and T3, 36, 16 and six patients, respectively; cN0 and N1, 57 and one patient, respectively. 55 (93%) patients received three cycles of chemotherapy with only mild toxicity. 46 (79%) patients received surgery and 42 (74%) had extrapleural pneumonectomy with a 90-day mortality of 6.5%. Post-operative radiotherapy was completed in 37 (65%) patients. Grade 3–4 toxicity persisted after 90 days in three (5.3%) patients. Median overall survival time was 18.4 months (95% CI 15.6–32.9) and median progression-free survival was 13.9 months (95% CI 10.9–17.2). Only 24 (42%) patients met the definition of success (one-sided 90% CI 0.36–1.00).

Although feasible, trimodality therapy in patients with mesothelioma was not completed within the strictly defined timelines of this protocol and adjustments are necessary.

KEYWORDS: Chemotherapy, malignant mesothelioma, phase II trial, prognosis, radiotherapy, thoracic surgery

Malignant pleural mesothelioma (MPM) is an aggressive neoplasm arising from the surface serosal cells of the pleural cavity. It is a highly lethal disease with a poor prognosis. The incidence of MPM has been predicted to increase rapidly in certain countries until approximately 2020 [1].

Different staging systems for MPM exist [2]. Although mainly related to surgical data, the TNM (tumour, nodes, metastasis)-based classification proposed by the International Mesothelioma Interest Group is the most widely used [3]. Precise determination of disease extent is difficult and response evaluation is even more complicated, as the classical criteria are not reliable. The use of perpendicular diameters, as proposed by BYRNE and NOWAK [4] in the modified Response Evaluation Criteria in Solid Tumours (RECIST), seems to be more accurate.

MPM has long been surrounded by therapeutic nihilism, as chemotherapy, radiotherapy and surgery have not been proven to be effective as a single treatment modality [1]. Moreover, the quality of published evidence is poor and no definite guidelines have been established, even for early-stage disease [5]. The role of surgery in providing maximal debulking is controversial and has not yet been determined [6, 7]. A major breakthrough was obtained with two randomised trials showing significant activity of the combination of cisplatin and a folate antagonist, pemetrexed or raltitrexed, with a significantly improved median survival time (MST) in patients with MPM [8–10]. Similar to locally advanced lung cancer, induction

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chemotherapy has been proposed to increase the complete resection rate of MPM. In a Swiss multicentre trial, cisplatin and gemcitabine were given as induction therapy followed by extrapleural pneumonectomy (EPP) and post-operative radiotherapy to incompletely resected areas [11]. For patients undergoing EPP, an encouraging MST of 23 months was obtained. The European Organisation for Research and Treatment of Cancer (EORTC) initiated a phase II trial to evaluate the feasibility of trimodality therapy in a multicentre international setting (EORTC protocol 08031).

PATIENTS AND METHODS

General objective and outline

The objective of the EORTC 08031 trial was to explore the feasibility of induction chemotherapy followed by EPP and high-dose, post-operative radiotherapy in patients with limited MPM. A general outline and CONSORT (Consolidated Standards of Reporting Trials) diagram are provided in figure 1. The protocol was approved by the ethical committees of each participating institution (see Acknowledgements section) and written informed consent was obtained from every patient.

End-points

Our primary end-point was ''success of treatment'', which is defined as a patient who received the full protocol treatment within the defined time-frames, and was still alive 90 days after the end of protocol treatment without progression or evidence of grade 3–4 toxicity. Secondary end-points included the toxicity of the trimodality treatment, overall survival and progression-free survival.

Patient selection criteria

General selection criteria are provided in table 1.

Therapeutic regimens

Chemotherapy

Induction chemotherapy consisted of three cycles of pemetrexed (500 mg·m^{-2}) and cisplatin (75 mg·m^{-2}) on day 1 every 3 weeks. Folic acid (350–600 μg *p.o.* daily) and vitamin B_{12} (1,000 μg *i.m.*) supplementation was started 7–14 days before the first dose of chemotherapy. Dexamethasone (4 mg *p.o.* twice daily) was administered on the day before, the day of and the day after each dose of chemotherapy. Folic acid was continued until 21 days after the last dose of chemotherapy and vitamin B_{12} injection was repeated on day 64.

Response assessment

Response was evaluated by repeat chest computed tomography (CT) according to the modified RECIST criteria [4]. Patients with a clinical response or stable disease underwent surgical resection.

Surgery

Surgery was performed 3–8 weeks after the last dose of chemotherapy. An EPP was performed in order to achieve a complete resection of all gross residual tumour. This included removal of the entire ipsilateral lung, parietal pleura, and also diaphragm and pericardium, which were both reconstructed with a soft tissue patch. Resectability was determined during thoracotomy.

Radiotherapy

Radiotherapy was initiated ⩾30 days after surgery but <84 days after surgery in patients who had recovered from surgery, with a World Health Organization (WHO) performance status of 0–2 and without disease progression on clinical examination and/or planing CT scan. Using three-dimensional (3D) conformal radiotherapy, a dose of 54 Gy was delivered to the entire hemithorax, thoracotomy incision and sites of chest drains in once-daily fractions of 1.8 Gy. A joined review of the contoured clinical target volume (CTV) with the thoracic surgeon was strongly recommended. The CTV included the entire ipsilateral thoracic cavity from lung apex to insertion of the diaphragm, ipsilateral mediastinal pleura, ipsilateral pericardial surface, and full thickness of the thorax at the sites of thoracotomy and chest drain incisions. The mediastinum was not routinely incorporated in the CTV,

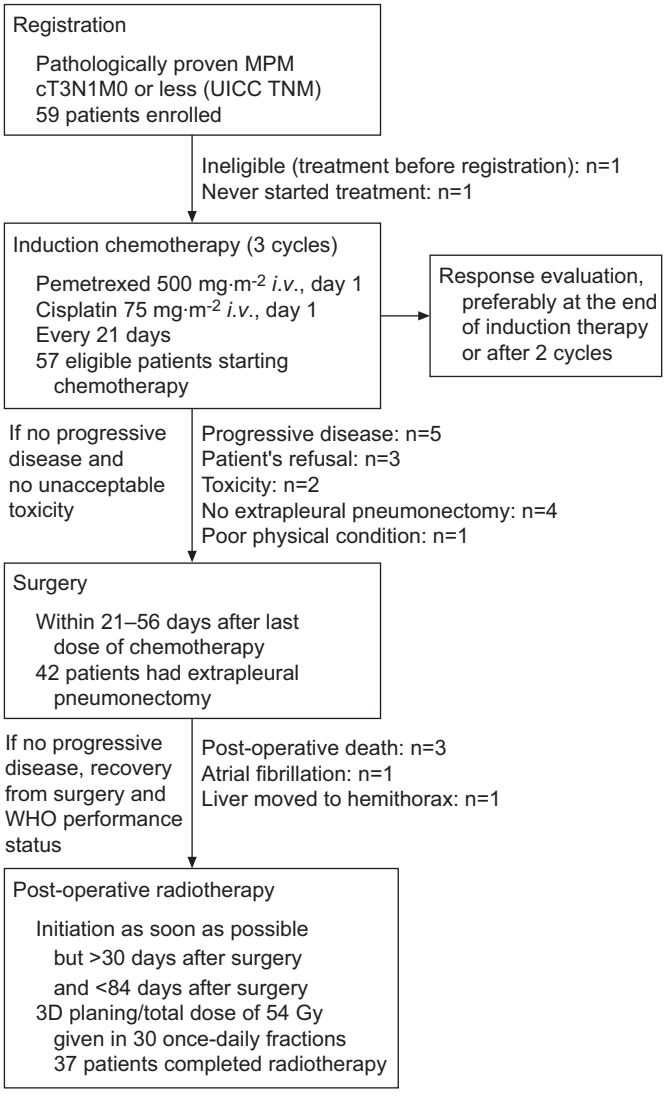

FIGURE 1. General outline and CONSORT (Consolidated Standards of Reporting Trials) diagram of the European Organisation for Research and Treatment of Cancer (EORTC) 08031 study. MPM: malignant pleural mesothelioma; UICC: International Union Against Cancer; TNM: tumour, nodes, metastasis; WHO: World Health Organization.

TABLE 1 Patient selection criteria

Age <70 yrs
WHO performance status 0–1
Fit enough to receive chemotherapy, to undergo a pneumonectomy and receive post-operative radiotherapy. The responsible physician, surgeon and radiation therapist judged the required fitness prior to registration, taking into account the results of all the relevant (*i.e.* pulmonary and cardiac) examinations. Proposed exclusion criteria were: predicted post-operative FEV_1 <40% and/or $V'_{O_2,max}$ <20 $mL \cdot min^{-1} \cdot kg^{-1}$, significant pulmonary hypertension, significant decrease in cardiac ejection fraction (<40%) and myocardium at risk of ischaemic injury.
Pathologically proven MPM (all subtypes accepted)
cT3N1M0 or less severe according to UICC TNM classification
No N2 or N3 lymph node involvement (pathologically confirmed), cervical mediastinoscopy required
No clinical invasion of mediastinal structures (heart, aorta, spine, oesophagus, *etc.*)
No widespread chest wall invasion, only focal chest wall lesions are acceptable
No clinical or radiological evidence of ''shrinking hemithorax''
No prior chemotherapy for mesothelioma
No prior radiotherapy of the lower neck, thorax or upper abdomen
No secondary or primary malignancy except *in situ* carcinoma of the cervix, adequately treated basal cell carcinoma of the skin or prior malignancy treated >5 yrs previously without recurrence
Adequate haematological, hepatic and renal function
Acceptable, predicted post-radiotherapy renal function, as indicated by semiquantitative isotope renography, with a relative contribution of the contralateral kidney of ⩾40%
No pre-existing sensory neurotoxicity greater than grade 1 according to CTCAE version 3.0 [12]
No clinically significant third-space fluid (*e.g.* pleural effusions or ascites) that cannot be managed with thoracentesis or pleurodesis (according to institutional practice)
No uncontrolled infection
Patients of reproductive potential were required to agree to use a reliable method of birth control during protocol treatment and for 3 months following the end of protocol treatment. Females of child-bearing potential were required to test negative for pregnancy at the time of enrolment, based on a serum pregnancy test
Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions were discussed with the patient before registration
Before patient registration, written informed consent was to be obtained and documented according to national and local regulatory requirements, and the local rules followed in the institution.

WHO: World Health Organization; FEV_1: forced expiratory volume in 1 s; $V'_{O_2,max}$: maximal oxygen uptake; MPM: malignant pleural mesthelioma; UICC: International Union Against Cancer; TNM: tumour, nodes, metastasis; CTCAE: Common Terminology Criteria for Adverse Events.

except at sites of proven disease. A boost CTV was given to sites of gross or microscopic residual disease. The V20, which is the volume of healthy lung tissue receiving a total dose of ⩾20 Gy, could not exceed 15%. Overall radiotherapy treatment time could not exceed 45 days.

Toxicity

Toxicity was scored according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 [12].

Follow-up

The follow-up visits were scheduled at 42 and 90 days after the administration of the last protocol treatment. Physical examination and evaluation of clinical symptoms and disease extent were performed by chest radiography and CT. Further follow-up was performed at 3-month intervals during the first year and every 6 months thereafter.

Statistics

To determine the success of treatment, a one-step Fleming testing procedure was used with α set at 0.10 and β at 0.05. P_0 was set at 40% and defined as the largest success rate that, if true, implied that this trimodality treatment did not warrant further investigation. P_1 was set at 60% and defined as the lowest success rate that, if true, implied that the trimodality treatment did warrant further investigation. Under these hypotheses, the total sample size was calculated to be 52 eligible patients; if a success rate of 60% were obtained in the study population, the combined trimodality treatment should be further investigated.

RESULTS

The study was opened in July 2005 and closed in August 2007. Accrual proceeded as planned. A CONSORT diagram is depicted in figure 1. In total, 59 patients were registered from 11 centres. One patient was ineligible because chemotherapy was started before registration. There were 46 male and 12 female patients with a median age of 57 yrs (range 26–67 yrs). All patients had pathologically proven MPM and underwent cervical mediastinoscopy. WHO performance status was 0 in 22 (37.9%) patients and 1 in 36 patients (62.1%). Known asbestos exposure was present in 44 (75.9%) patients. Clinical T stage at baseline was T1 in 36 (62.1%) patients, T2 in 16 (27.6%) patients and T3 in six (10.3%) patients. Clinical N stage was N0 in 57 (98.3%) patients and N1 in one (1.7%) patient. Associated chronic disease was present in 18 (31.0%) patients, mainly hypertension and diabetes. One registered patient refused any treatment after obtaining a second opinion.

Chemotherapy

In 55 (94.8%) patients, three cycles of chemotherapy were administered and in three (5.2%) patients, two cycles. Three patients received carboplatin instead of cisplatin. Median (range) relative dose intensity of cisplatin was 98.9% (75.1–106.8%) and

of pemetrexed 99.5% (range 75.4–104.2%). Cisplatin dose reduction was necessary in four (6.9%) patients due to fatigue, neuropathy, nausea, combined hearing loss and increased creatinine levels, and of pemetrexed in only one (1.7%) patient, due to fatigue. Grade 3–4 toxicity is listed in table 2. In eligible patients who started treatment (57 (96.6%) patients), radiological response after chemotherapy was complete in 14 (24.6%) patients, partial in 11 (19.3%) patients, stable in 24 (42.1%) patients, progressive in five (8.8%) patients and not assessable in three (5.3%) patients.

Surgery

In the 58 eligible patients, surgical treatment was administered in 46 (79.3%) patients. 12 (20.7%) patients had no surgery because of progressive disease (8.6%), poor physical condition (1.7%), toxicity (1.7%), pulmonary emboli (1.7%) and no initiation of therapy after a second opinion (6.9%).

Pre-operative lung function showed a median forced expiratory volume in 1 s of 76.0% predicted (range 50.0–115.0%), a median forced vital capacity of 80.0% pred (range, 43.0–116.0%) and median diffusing capacity of the lung for carbon monoxide of 71.0% (range 35.0–112.0%). In 33 (71.7%) patients who received surgery, the tumour was on the right side and in 13 (28.3%) patients, on the left side. EPP was performed in 42 patients (91.3% of patients who received surgery and 73.7% of eligible patients who started treatment). The other patients had partial pleurectomy or exploration due to unresectable disease only.

R0 resection was obtained in 30 patients (52.6% of eligible patients who started treatment), R1 in 10 (17.5%) patients, R2 in three (5.3%) patients and unknown in one (1.8%) patient. Re-operation was necessary in six patients because of bronchopleural fistula (n=2), post-operative haemorrhage (n=2), infection at the thoracotomy incision (n=1) and diaphragmatic eventration (n=1). Mortality at 30 and 90 days was 6.5% due to pulmonary embolism, combined lung oedema and pneumonia, and progressive disease. Post-operative complications were observed in 38 (82.6%) patients, mostly supraventricular arrhythmias. Grade 3–4 complications are listed in table 2.

Pathological T0 was observed in two patients, T1 in five patients, T2 in 19 patients, T3 in 15 patients and T4 in four patients. Pathological N0 was present in 35 patients, N1 in two patients, N2 in six patients and Nx in two patients.

After central pathological review, 31 (53.4%) patients had epithelial cell type, 18 (31.0%) patients mixed histology, two (3.4%)

TABLE 2 Grade 3–4 toxicity after chemotherapy, surgery and radiotherapy

	Chemotherapy	Surgery	Radiotherapy
Subjects	57	46	38
Haematological and biochemical			
Leukopenia	1 (1.8)		
Anaemia	1 (1.8)	4 (8.7)	
Neutropenia	9 (15.5)		
Hyponatraemia	3 (5.2)		
Hyperkalaemia	2 (3.4)		
Anorexia		1 (2.2)	2 (5.3)
Dysphagia			1 (2.6)
Nausea			2 (5.3)
Vomiting			1 (2.6)
Fatigue	1 (1.8)		2 (5.3)
Infection	2 (3.6)	1 (2.2)	
Pneumonia		2 (4.3)	
Pain	3 (5.4)	3 (6.5)	1 (2.6)
Dyspnoea	2 (3.6)	5 (4.7)	1 (2.6)
Renal toxicity	1 (1.8)		
Septic shock	1 (1.8)		
Thromboembolism	2 (3.6)		
Atrial fibrillation	1 (1.8)	4 (8.7)	
Cardiac other		4 (8.7)	
Retinal detachment	1 (1.8)		
Empyema		1 (2.2)	
Haemorrhage requiring reoperation		2 (4.3)	
Bronchopleural fistula		2 (4.3)	
Post-pneumonectomy pulmonary oedema		2 (2.2)	
Vascular (other)		1 (8.7)	
Other#		4	

Data are presented as n or n (%). #: includes post-operative stroke (n=1), obstipation (n=1) and haemorrhage not requiring reoperation (n=2).

patients unknown and data is missing for seven (12.1%) patients. Complete agreement with local pathologist was present in 38 (65.5%) cases, minor disagreement in 10 (17.2%) cases and full disagreement in three (5.2%) cases.

Radiotherapy

Post-operative radiotherapy was initiated in 38 patients and completed in 37 (63.8% of all eligible patients). In 11 patients, administration of radiotherapy was temporarily interrupted. Intensity-modulated radiotherapy was given in 14 patients and 3D conformal radiotherapy in 24 patients. Median radiotherapy dose was 54.0 Gy (range 43.2–54.0 Gy). In 18 patients, a chest wall bolus was given. Median V20 to the contralateral lung was 2.0% (range 0.0–30.4%). Median maximum dose to spinal cord was 43.3 Gy (range 9.5–52.5 Gy). Two patients died after radiotherapy due to pneumonia, one having *Aspergillus* infection. Grade 3–4 toxicity of radiotherapy is listed in table 2.

Follow-up

Trimodality treatment was completed in 37 (64.9%) patients and median treatment duration was 184 days. Median follow-up time was 19.3 months (95% CI 17.4–25.0). Grade 3–4 toxicity 90 days after the end of the treatment protocol persisted in three (5.7%) patients due to bronchopleural fistula (n=2) and grade 3 radiation pneumonitis (n=1). Recurrences detected during follow-up were locoregional in six (16.2%) patients and distant metastases in 10 (27%) patients.

Only 24 (42.1%) patients met the primary end-point definition of success (one-sided 90% CI for proportion of success 0.36–1.00). Reasons for failure are listed in table 3. If some flexibility is allowed by relaxing the treatment timelines only, there are four additional patients who can be considered a success. Performing a supplementary sensitivity analysis in all 57 patients who were eligible and started treatment, the total number of successes becomes 28 if these four patients are added. The corresponding one-sided 90% CI is 0.399–1.00. This is in the borderline of declaring the study a success.

Median overall survival time for all 57 patients who were eligible and started treatment was 18.4 months (95% CI 15.6–32.9) and 1-yr survival rate 70.2% (95% CI 56.5–80.3) (fig. 2). Median progression-free survival for all 57 patients who were eligible and started treatment was 13.9 months (95% CI 10.9–17.2) and 1-yr survival rate 54.4% (95% CI 40.7–66.2) (fig. 3).

TABLE 3 Primary end-point: reasons for failure

Reason	Subjects n
⩾2 cycles of chemotherapy not given	1
No extrapleural pneumonectomy	15
No 54 Gy post-operative radiotherapy	21
Treatment not within time frame	27
Mortality	7
Persisting grade 3–4 toxicity	3
Progressive disease	16

Data for all registered patients; some patients had multiple reasons for not reaching the primary end-point.

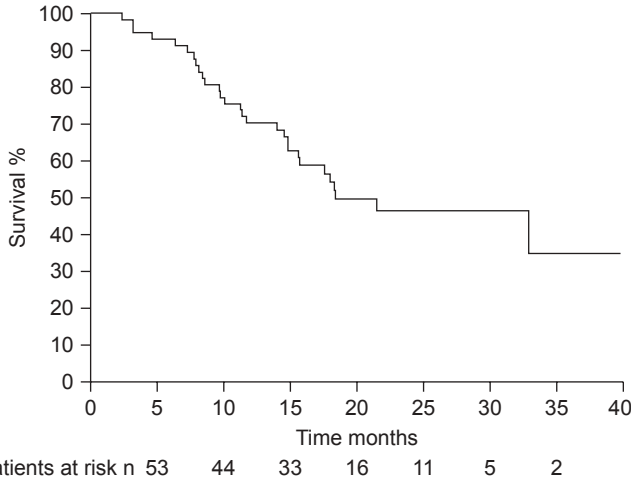

FIGURE 2. Overall survival for all 57 patients who were eligible and started treatment. 29 events were observed.

Median overall survival time for the 37 patients who completed trimodality treatment was 33 months. The median was hardly reached and longer follow-up is needed in these patients to obtain a more precise figure.

DISCUSSION

The role of surgical treatment in patients with MPM remains controversial. This relates to the indications and extent of surgical resection [5, 6]. In selected patients, EPP provides maximal tumour clearance with an acceptable mortality and morbidity in specialised centres [13, 14]. In a compiled series from three large institutions, 663 patients undergoing EPP or pleurectomy/decortication in 1990–2006 were analysed [15]. Operative mortality was 7% for EPP and 4% for pleurectomy/decortication. Significant factors related to survival were disease stage, epithelial cell type, type of resection, multimodality therapy and sex. Although less radical, pleurectomy/decortication has emerged as a potential debulking procedure,

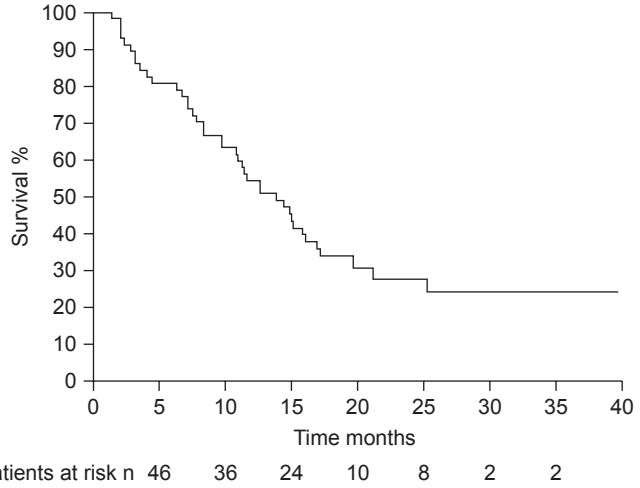

FIGURE 3. Progression-free survival for all 57 patients who were eligible and started treatment. 40 events were observed.

TABLE 4 Prospective multicenter phase II trials of radical multimodality treatment in early stage malignant pleural mesothelioma

Variable	SAKK trial [11]	USA phase II trial [20]	EORTC 08031
Patients/institutions n/n	61/6	77/9	59/11
Induction regimen	Cis–gem ×3	Cis–pem ×4	Cis–pem ×3
Compliance to induction chemotherapy	95	83	93
EPP	45 (74)	54 (70)	42 (74)
Operative mortality	2.2	7	6.5
pCR rate	2.2	5	4.8
PORT completed	36 (59)	40 (52)	37 (65)
OS months			
ITT	19.8 (14.6–24.5)	16.8 (13.6–23.2)	18.4 (15.6–32.9)
PP	23.0 (16.6–32.9)	21.9 (16.8–29.1)	21.5 (17.6–NR)
Local relapse n (% PP)	NS	11 (28)	6 (16)
PFS months			
ITT	13.5 (10.2–18.8)	10.1 (8.6–15.0)	13.9 (10.9–17.2)
Median overall treatment time (range) days	NS	NS	193 (162–220)

Data are presented as %, n (%) or median (95% CI), unless otherwise stated. SAKK: Swiss Group for Clinical Cancer Research; EORTC: European Organisation for Cancer Research and Treatment; EPP: extrapleural pneumonectomy; pCR: pathologically complete response; PORT: post-operative radiotherapy; OS: overall survival; ITT: intention to treat; PP: per protocol; PFS: progression-free survival; Cis: cisplatin; gem: gemcitabine; pem: pemetrexed; NR: not reached; NS: not stated.

not only providing better palliation but also improved local control and possibly even survival [16, 17].

Due to the ineffectiveness of single-modality therapy in patients with MPM, trimodality therapy has recently emerged as a new treatment strategy to improve prognosis [18]. To improve resectability rate and local control, induction chemotherapy is combined with aggressive surgery and post-operative radiotherapy. Pemetrexed has been shown to be among the most active agents and is currently used in induction trials [9]. In a retrospective study of 60 patients, four regimens of induction chemotherapy were used [19]. EPP was performed in 54 patients (75%) followed by hemithoracic radiotherapy in 30 (50%) patients. The best survival was noted in those patients without mediastinal nodal involvement who completed the trimodality therapy. For patients with N0 disease, 5-yr survival rate was 53%.

Although the introduction of pemetrexed was a major step forward in the palliative treatment of mesothelioma patients, current results are unlikely to improve further without the addition of targeted or biological agents interacting more specifically with causal pathways in the cellular behaviour of mesothelioma. No such agent is currently available for association with induction chemotherapy.

In contrast to other tumour types and nonsmall cell lung cancer, the current induction chemotherapy regimens induce little necrosis and pathological complete responses, questioning their presumed role in facilitating resection and reducing their efficacy of clearing micrometastatic disease. As such, their adjuvant administration might merit further attention in radically resected patients having completed post-operative radiotherapy.

The primary end-point was not reached in our study as only 24 (42.1%) patients were a success according to the predefined criteria. *Post hoc*, these criteria might be considered unrealistic, but they were predefined arbitrarily in 2003 by an expert multidisciplinary committee within the EORTC Lung Cancer Group and considered a minimum in order to proceed further with trimodality treatment in this disease.

Nevertheless, the results of EORTC 08031 merit further consideration for a number of reasons. Its overall results confirm the outcome of two comparable multicentre phase II trials with multimodality treatment [11, 20]. Their end-points of survival, mortality, response rate and compliance to induction chemotherapy are comparable to the ones observed in EORTC 08031, suggesting that their success of treatment as defined in EORTC 08031 will probably be equivalent (table 4).

In a subsequent sensitivity analysis, relaxing somewhat the strict timeline criteria, a number of additional patients met all other criteria and can be considered successes, increasing the likelihood of the study meeting its end-point.

Although the multimodality treatment procedure seems feasible, overall treatment time is long and the median duration of psychological distress consumes much of the observed improvement of survival. Subgroup analysis of a large Scandinavian phase II trial showed an survival of 22 months in patients with good performance status, epithelioid subtype, stage I–II disease and age $\leqslant$70 yrs, equivalent to the survival in patients subjected to multimodality treatment [21]. This finding underscores the importance of conducting a large, prospective multicentre study, in which operable patients with early-stage, resectable MPM are randomly assigned to surgical and nonsurgical management [22]. The feasibility of this approach is currently being explored in the Mesothelioma and Radical Surgery (MARS) trial in the UK, in which the randomisation is between EPP followed by post-operative radiotherapy and any palliative treatment including pleurodesis, following an induction treatment with chemotherapy. A pilot trial has recently been completed and randomisation between surgery and no surgery was found to be feasible [23].

The conclusion from uncontrolled series that pleurectomy/decortication might prolong survival suggests that EPP is perhaps not the only procedure to be considered as a surgical approach and that a less invasive procedure might be preferable in selected patients, provided it is standardised [24]. It is expected that a large European multicentre randomised trial will be conducted in the future, addressing the role of any tumour resection in MPM. Whether it will include EPP remains to be determined, as the median age at presentation increases and the drop-out rate will be considerable [25].

As in nonsmall cell lung cancer, the role of post-operative radiotherapy in MPM is controversial and based on a single, uncontrolled retrospective series [26]. This additional value of post-operative radiotherapy is being addressed in an ongoing Swiss study, in which eligible patients are randomised after EPP between observation and hemithoracic radiotherapy [27]. Preliminary results of intensity modulated radiotherapy (IMRT) in the adjuvant setting after EPP seems particularly promising, as good local control was obtained and organs at risk, such as heart or liver, were well protected [28]. However, severe pulmonary toxicity has been reported in recent studies; therefore, it should not be recommended outside clinical trials [29]. The role of IMRT with chemotherapy and intact lung is presently being investigated in patients with unresectable disease [30].

In conclusion, although a trimodality treatment consisting of induction chemotherapy followed by extrapleural resection and post-operative radiotherapy seems feasible in selected patients with early stage mesothelioma, the results of the present study do not warrant its use outside selected institutions with high levels of expertise and, preferably, in prospective clinical trials exploring ways to improve its acceptance rate and overall success.

SUPPORT STATEMENT

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CLINICAL TRIAL

This study is registered with clinical trial identifier numbers EudraCT-2004-004273-28 and NCT00227630. This study is also registered with the EORTC, protocol 08031.

STATEMENT OF INTEREST

A statement of interest for J.P. van Meerbeeck and the study itself can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

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