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BTS randomised feasibility study of active symptom control with or without chemotherapy in malignant pleural mesothelioma: ISRCTN 54469112

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Background: The incidence of mesothelioma is rising rapidly in the UK. There is no generally accepted standard treatment. The BTS recommends active symptom control (ASC). It is not known whether chemotherapy in addition prolongs survival or provides worthwhile palliation with acceptable toxicity. Palliation as recorded by patients has been fully reported for only two regimens: mitomycin, vinblastine, and cisplatin (MVP), and vinorelbine (N). The BTS and collaborators planned to conduct a phase III randomised trial comparing ASC only, ASC+MVP, and ASC+N in 840 patients with survival as the primary outcome measure. The aim of the present study was to assess the acceptability of the trial design to patients and the suitability of two standard quality of life (QL) questionnaires for mesothelioma.

Methods: Collaborating centres registered all new patients with mesothelioma. Those eligible and giving informed consent completed EORTC QLQ-C30+LC13 and FACT-L QL questionnaires and were randomised between all three or any two of (1) ASC only, (2) ASC+4 cycles of MVP, and (3) ASC+12 weekly doses of N.

Results: During 1 year, 242 patients were registered of whom 109 (45%) were randomised (55% of the 197 eligible patients). Fifty two patients from 20 centres were randomised to an option including ASC only. This translates into a rate of 312 per year from 60 centres interested in collaborating in the phase III trial. The EORTC QL questionnaire was superior to FACT-L in terms of completeness of data and patient preference. Clinically relevant palliation was achieved with ASC.

Conclusion: The planned phase III trial is feasible.

Malignant mesothelioma is almost invariably fatal and its incidence is rising rapidly. In the UK the age standardised death rate per 100 000 rose from 0.33 in 1970–4 to 1.20 in 1990–4, and it is estimated that the annual number of deaths from mesothelioma will rise from approximately 1500 in the year 2000 to a peak of approximately 3000 in 2020.[1 2] The highest incidence is seen in men born in 1945–50, reflecting the extent of use of asbestos in the 1960s and 1970s at the beginning of their working lives.

There is no generally agreed standard treatment for unresectable mesothelioma. According to BTS recommendations at the time the present study was planned and conducted, patients should be treated with ''active symptom control'' (ASC) involving: (1) regular specialist follow up, (2) structured assessment of physical, psychological and social problems with appropriate treatment, which can include pleurodesis, palliative radiotherapy and steroids, (3) rapid referral to additional specialists when required, and (4) parallel nursing support.[3]

Clinicians disagree on whether any anticancer chemotherapy prolongs survival or provides worthwhile palliation with acceptable toxicity when given in addition to ASC. Numerous small non-randomised studies of various single drug and multidrug regimens have shown that a number have activity against mesothelioma, and a review of studies involving 15 or more patients made the following observations:[4]

- The role of systemic chemotherapy should be regarded as an area of investigation.
- Various single agents have shown temporary partial response rates of around 20%, although response is difficult to measure in mesothelioma because of the diffuse nature of this tumour.
- There is no persuasive evidence that drug combinations are more active than single drugs.
- Randomised trials are needed to confirm activity, to investigate clinical usefulness, and to determine whether responses translate into prolonged survival.

Response rates do not necessarily reflect symptom relief, which is more important for patients with an incurable disease. At the time when this study was planned, good data on symptom control from patients' questionnaires were available for only two regimens. Middleton and colleagues treated 39 patients with six cycles of mitomycin, vinblastine and cisplatin (MVP) repeated every 21 days.[5] In all, 62% of patients had an overall improvement in their symptoms, palliation being particularly good for pain (79%) and cough (67%). Palliation was achieved in all of the 20% of patients showing a partial tumour response, but worthwhile symptom control was also seen in some of those without such response. The regimen was well tolerated. Steele and colleagues treated 29 patients with single drug vinorelbine (N) every 7 days until disease progression.[6] Improvement in respiratory symptoms was reported by 48% of patients and in psychological functioning by 76%. The regimen was well tolerated.

In a systematic review of the literature, trial databases, colleagues, and the pharmaceutical industry, we found three published randomised trials,[7–9] but all three were small (32, 76, and 79 patients, respectively) and compared one chemotherapy regimen with another. There were three more

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closed but as yet unpublished randomised trials. One (EST-1380) compared postoperative radiotherapy with or without doxorubicin; the second (NCI-93-0204C) debulking surgery + chemo-immunotherapy with or without intrapleural photodynamic therapy; and the third (Lilly Oncology, NCI-G00-1767) cisplatin with or without multitargeted folate antagonist (pemetrexed) in 456 patients. Thus, no other randomised trial has included an ASC only group.

A large randomised phase III trial is needed to assess whether, in the treatment of malignant pleural mesothelioma, chemotherapy with MVP or N in addition to ASC is better than ASC alone in terms of overall survival, symptom palliation, performance status, analgesic usage, toxicity, quality of life (QL), tumour response, and progression-free survival. Before embarking on such a trial we conducted the present feasibility study to assess the acceptability of the randomisation to patients and the suitability of the EORTC QLQ-C30+LC13 and the FACT-L QL questionnaires in mesothelioma.

METHODS

Patients

In collaborating centres all new patients with a diagnosis of mesothelioma were registered with the MRC Clinical Trials Unit. Registered patients were eligible for randomisation if they fulfilled the following criteria:

- microscopically and immunohistochemically confirmed malignant pleural mesothelioma, including epithelial and other histological types;
- any symptomatic pleural effusion under control by drainage, pleurodesis, or pleurectomy;
- a CT scan within 1 month before randomisation (preferably after pleurodesis);
- if mesothelioma resected, two CT scans 6 weeks apart showing assessable stable or progressive disease;
- no previous chemotherapy for mesothelioma;
- no other disease likely to interfere with protocol treatments or comparisons;
- WHO performance status 0–2;[10]
- white blood cell count $>3 \times 10^9$/l, neutrophil count $>1.5 \times 10^9$/l, platelet count $>100 \times 10^9$/l, and no clinical evidence of infection;
- medically fit to receive chemotherapy;
- informed consent form signed following full discussion of a patient information sheet describing the study design and stating that the doctor would discuss with the patient which comparison was most suitable;
- quality of life forms completed before patient told the treatment allocated.

Multicentre Research Ethics Committees (MREC) approval of the protocol was obtained. Confirmation of Local Research Ethics Committee's (LREC) approval was required before a centre could start registering patients.

Treatment groups

Clinicians were encouraged to randomise eligible patients between all three treatment groups: (1) ASC only; (2) ASC+MVP; (3) ASC+N, but were allowed to offer patients randomisation between any two. This choice was permitted to ensure a good measure of the acceptability of the ASC only arm to both patients and clinicians.

Active symptom control (ASC)

The essential elements were as follows:

- Regular follow up in a specialist clinic by an identified physician or team.
- Structured assessments at every clinic visit of physical, psychological, and social problems with appropriate treatment or other action.
- Rapid involvement of additional specialists such as a pain relief service, specialist palliative care team, medical social worker, or physiotherapist. (It was recommended that patients with pain not easily controlled by a combination of slow release morphine and co-analgesics be referred to a pain relief service.)
- Parallel nursing support from a named specialist nurse or similar person.

ASC could include treatment with palliative radiotherapy and steroids.

Mitomycin, vinblastine, and cisplatin (MVP)

Mitomycin 8 mg/m^2 by bolus intravenous injection, vinblastine 6 mg/m^2 (maximum dose 10 mg) by bolus intravenous injection, and cisplatin 50 mg/m^2 by intravenous infusion over 4 hours were given every 21 days for a total of four cycles with standard hydration and anti-emetics.

Vinorelbine (N)

Six intravenous injections at weekly intervals followed by a 2 week break before a further six injections at weekly intervals of vinorelbine 30 mg/m^2 (maximum dose 60 mg) were given, with standard anti-emetics.

QL questionnaires

All patients completed EORTC QLQ-C30+LC13[11] and FACT-L[12] QL questionnaires. To avoid bias that may arise if one questionnaire is always completed before the other, the sequence in which they were completed was randomised by centre, the sequence remaining the same for every assessment of all patients from that centre.

Assessments

Pretreatment assessments included a CT scan of the thorax; the QL questionnaires had to be completed before the patients were told their treatment group. During the treatment period, when MVP and N patients were receiving chemotherapy, all patients were assessed clinically every 3 weeks. Thereafter, patients were assessed every 8 weeks until death. QL questionnaires were completed immediately before all assessments. A CT scan was performed at the end of chemotherapy or 3–4 months after randomisation in the ASC only group.

Statistical methods

The outcome measures were the acceptability of the study design to patients, suitability of the EORTC QLQ-C30+LC13 and FACT-L QL questionnaires for mesothelioma, and palliation. Acceptability of the design was measured by the proportions of registered patients accepting randomisation and of randomised patients accepting ASC only as one of their randomisation options. The suitability of the QL questionnaires was assessed by compliance with their use and patient preference: patients were asked to state their preferred QL questionnaire but were not asked their reasons. Palliation was measured in terms of WHO performance status[10] and severity of chest pain, breathlessness, anorexia, and sweating (present "not at all" = 0, "a little" = 1, "quite a bit" = 2, or "very much" = 3). Palliation was defined as: (1) improvement (change from a score of 2 or 3 to 0 or 1), (2) control (a score of 1 not getting worse), and (3) prevention (a score of 0 being maintained)[13] from baseline to 16 weeks after randomisation, based on clinicians' assessments. The study was not powered to compare tumour response or survival between treatment groups; these outcome measures

are therefore not reported but are included in the phase III trial.

RESULTS

Acceptability of the trial design

From September 2000 to September 2001, 242 patients were registered from 46 UK centres. Of the 197 eligible for randomisation, 109 from 35 centres were randomised, 55% (95% CI 48 to 62) of those eligible and 45% of those registered. The main reasons for non-randomisation were ineligibility and patient refusal (table 1).

The randomisation options are shown in table 2. A third of patients were randomised to the recommended option (between all three treatment groups), but the option included ASC only in 52 (48%) of the 109 patients (95% CI 38 to 57), these 52 being randomised from 20 centres. With an eventual rate of randomisation including ASC only of 8.7 patients per month (104 per year), this translates into an estimated rate of 312 (104 × 3) per year from the 60 centres that expressed an interest in collaborating in the phase III trial.

The characteristics of the patients at registration or randomisation according to their randomisation group are shown in table 3. The three groups of patients (randomised with ASC only option, randomised without ASC only option, not randomised) were very similar except that there was a tendency for the group randomised without the ASC only option to be younger than the group with this option (median age 61 and 66 years, respectively).

Comparison of the two QL questionnaires

Compliance with the completion of the QL questionnaires was similar (table 4) but with a higher rate of missing responses per question with the FACT-L (9.1%) than with the EORTC QLQ-C30+LC13 (6.9%). Questionnaire preference was expressed on 386 forms. Although on 291 (75%) occasions patients expressed no preference between the questionnaires, on 75 occasions (19%) they preferred the EORTC QLQ-C30+LC13 questionnaire and on 20 occasions (5%) the FACT-L questionnaire was preferred.

Palliation of symptoms

The analysis of palliation of symptoms was based on patients assessed before treatment and with more than one subsequent assessment during the first 16 weeks after randomisation, or who died during the 16 weeks but with at least one assessment after randomisation. Patients treated with ASC only were compared with those treated with ASC plus any chemotherapy (table 5). There is a suggestion that palliation was better with chemotherapy than without, but there is evidence that clinically useful levels of palliation were achieved with ASC only (28% for chest pain, 11% for breathlessness, 44% for anorexia, and 67% for sweating attacks). It is important to note, however, that the study was not powered to make reliable comparisons between treatment groups. All the patients had WHO performance status grades 0, 1, or 2 before treatment. In both patient groups these levels changed very little during the first 16 weeks (details not shown).

Table 1 Reasons for non-randomisation among all 242 registered patients

Reason	Patients, n (%*)
Not eligible	45 (34)
Eligible, patient refusal	47 (36)
Clinician's decision	29 (22)
Other	11 (8)
Reason not known	1
Total not randomised	133

*Percentage of the 132 patients for whom the reason is known.

Table 2 Randomisation options for all 109 randomised patients

Options	Patients, n (%)
ASC versus MVP versus N	35 (32)
ASC versus MVP	2 (2)
ASC versus N	15 (14)
MVP versus N	57 (52)
All those including ASC only	52 (48)

ASC = active symptom control; MVP = mitomycin, vinblastine and cisplatin; N = vinorelbine.
ASC = ASC only; MVP = ASC+MVP; N = ASC+N.

DISCUSSION

This feasibility study has shown that, in the treatment of malignant pleural mesothelioma, randomisation to ASC with or without chemotherapy was sufficiently acceptable to patients and clinicians for a large multicentre randomised trial comparing ASC only versus ASC+MVP versus ASC+N to be feasible. Of the patients eligible for randomisation, 55% were randomised between all three or any two of the treatment groups, half of whom accepted a randomisation option including ASC only. Indeed, intake to a multicentre cancer research UK trial (MS01) in which all patients are being randomised between all three treatment groups is now underway and is currently attracting support from 52 centres. At the time we made our grant application for the phase III trial, 60 centres that expressed an interest estimated that between them they could randomise more than 400 patients per year. Allowing for overestimation, we plan to recruit a total of 840 patients (280 per treatment group) during 4 years, including those already randomised between the three treatment groups in the present feasibility study. The current mean rate of accrual is three patients per centre per year.

Crucial to the study of the possible roles of chemotherapy in the treatment of mesothelioma, a cancer relatively resistant to chemotherapy, is the study of quality of life as reported by patients. Only in this way can the possible benefits and adverse effects be adequately assessed. An important finding from the present feasibility study is therefore the suitability of the EORTC QLQ-C30+LC13 questionnaire for use in patients with pleural mesothelioma, and this instrument is being used in the subsequent MS01 phase III trial.

The study was not powered to make reliable comparisons between the treatment groups, but an important finding is that clinically relevant levels of palliation were achieved with ASC only. It is therefore important to establish whether chemotherapy improves palliation compared with ASC.

After the intake to the MS01 trial had started, results of the randomised trial comparing cisplatin with or without pemetrexed (ALIMTA) in 456 patients were presented at the 2002 Annual Conference of the American Society of Clinical Oncology and appeared to show a survival advantage for pemetrexed + cisplatin over cisplatin alone.[14] The question therefore arose whether intake to the MS01 trial should continue. We decided that it should for the following reasons. Firstly, the pemetrexed trial has only been presented and the findings were not included in the published abstract; details of its design, methods, analyses, and findings are therefore not yet publicly available and have not been peer reviewed. Secondly, pemetrexed is not yet available in the UK and is unlikely to be so for at least 2 years. Thirdly, the data presented showed that the pemetrexed trial design was

Table 3 Characteristics of patients according to randomisation group

Characteristic	Randomised: With ASC only option, n (%)	Randomised: Without ASC only option, n (%)	Not randomised* n (%)
Age			
<60	13 (25)	24 (42)	29 (22)
60–69	19 (37)	26 (46)	46 (35)
70+	20 (39)	7 (12)	58 (44)
Median (range)	66 (48–80)	61 (38–78)	69 (43–87)
Sex			
Male	47 (90)	46 (81)	111 (83)
Female	5 (10)	11 (19)	22 (17)
Histology			
Epithelial	40 (77)	43 (75)	NA
Other	12 (23)	14 (25)	NA
Performance status			
0	5 (10)	8 (14)	NA
1	33 (64)	35 (61)	NA
2	14 (27)	14 (25)	NA
Total patients	52	57	133

*These patients were simply registered; information on histology and performance status was not collected.

Table 4 Compliance with completion of quality of life questionnaires

Compliance	EORTC QLQ-C30+LC13	FACT-L
Number of questionnaires expected	798	798
Number of questionnaires received	578	584
Number of questions per questionnaire	44	38
Number of missing items	1747	2024
Mean number of missing items per questionnaire	3.0	3.5
Mean missing rate per question	6.9%	9.1%

changed during patient recruitment because of high toxicity and death rates in the pemetrexed arm. Full vitamin B12 and folate supplementation was introduced part way through for all subsequent patients. This reduced the toxicity and death rates and the planned number of patients was increased. The survival difference in the fully vitamin supplemented patients was of borderline significance ($p = 0.051$) and eight patients were excluded from this analysis (that is, it was not done by intention to treat). Fourthly, the median age was lower (61 years) and the performance status of the patients higher (only ECOG 0–1 eligible) than those typically seen in patients in the UK and, indeed, in the current feasibility study. It is therefore uncertain whether similar results would be achievable in UK practice. Finally, it is questionable whether single drug cisplatin, in a moderately high dose (75 mg/m^2) for up to six cycles, is an appropriate control: it achieved, as expected, a low response rate (17% according to non-standard criteria); it gave rise to 6% grade 3 or 4 vomiting and 2% drug related deaths; and it was associated with increasing pain and dyspnoea during treatment. It could well be that, at least in terms of quality of life, ASC as given in the present study is superior, especially in the light of the palliation it achieved.[15] A recent systematic review of published phase II studies concluded that the role of chemotherapy for unresectable malignant mesothelioma is unclear but that the combination of cisplatin and doxorubicin should be considered as a control for randomised

Table 5 Palliation of symptoms during the first 16 weeks after randomisation*

Nature of palliation†	ASC only: Assessable	ASC only: Palliated	ASC plus chemotherapy: Assessable	ASC plus chemotherapy: Palliated
Chest pain				
Improvement	9	2	22	12
Control	7	2	26	16
Prevention	2	1	36	16
Total palliated	18	5 (28%)	84	44 (52%)
Breathlessness				
Improvement	7	0	24	7
Control	9	1	29	14
Prevention	2	1	16	2
Total palliated	18	2 (11%)	83	23 (28%)
Anorexia				
Improvement	4	0	12	7
Control	4	4	11	6
Prevention	10	4	61	30
Total palliated	18	8 (44%)	84	43 (51%)
Sweating attacks				
Improvement	4	2	18	9
Control	3	3	19	12
Prevention	11	7	47	32
Total palliated	18	12 (67%)	84	53 (63%)

*This analysis was based on clinicians' assessments from which more data were available than from the questionnaires, but the results are very similar to those from the patient questionnaires.
†Defined in the text.

trials.[16] This recommendation was, however, based solely on response rates.

Confidential interim analyses from the MS01 trial will continue to be regularly reviewed by its independent data monitoring and ethics committee. Moreover, this committee is also reviewing results of the pemetrexed trial as they emerge and can recommend changes to the MS01 protocol if and when it considers these to be ethically desirable.

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