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Malignant Mesothelioma: Clinical Characteristics, Asbestos Mineralogy and Chromosomal Abnormalities of 41 Patients

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The clinical characteristics and the results of mineral fibre and cytogenetic analyses were coordinated prospectively for 41 patients with confirmed malignant pleural mesothelioma. A correlation was found between high total fibre concentration, and partial or total loss of chromosomes 1, 4 and 9 and chromosomal rearrangements involving a breakpoint at 1p11–p22. There was also a correlation between crocidolite/amosite as the main fibre type and partial or total loss of chromosomes 1, 3 and 4 and chromosomal rearrangements involving del (3p). Positive prognostic factors were female gender, low total fibre concentration (< 10^6 fibres per g dried lung tissue), anthophyllite as the main fibre type and normal chromosome 7. In addition, we found 4 patients with malignant mesothelioma who had been exposed mainly to anthophyllite fibres (total lung fibre concentrations of 1.2, 0.4, 0.2 and 0.1 × 10^6 fibres per g dried lung tissue). This would seem to indicate that there may be a carcinogenic role for anthophyllite.
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ASBESTOS EXPOSURE and possibly genetic susceptibility are considered to be contributing factors in the development of malignant mesothelioma [1, 2]. The latent period, between the first exposure to asbestos and the diagnosis of mesothelioma ranges from 20 to 40 years. This explains the increasing incidence of mesothelioma in industrialised countries, with the highest incidence occurring in people who suffered heavy occupational exposure between 1950 and 1970 [3]. In Finland, the annual incidence of mesothelioma in 1985 was 12 per million for males and 3 per million for females [4]; but as yet very little is known about the natural history and biology of the disease.

Amphibole fibres with a high length-to-diameter ratio such as crocidolite, amosite and tremolite are most often implicated in the development of mesothelioma [5, 6]. Chrysotile, by comparison, is less carcinogenic, and anthophyllite has not been shown to cause mesothelioma in exposed individuals [7]. In Finland, anthophyllite asbestos has been mined and used in exceptionally large quantities in the construction industry; it is estimated that 200 000 workers had significant exposure between 1918 and 1975 [7]. It was therefore of particular interest to study prospectively more Finnish mesothelioma patients, in order to elucidate further the possible relationship between anthophyllite and mesothelioma, and to characterise biologically such anthophyllite related tumours.

Experimental studies have shown that asbestos fibres cause cell transformation and chromosomal abnormalities in normal human mesothelial cells [8]. Non-random patterns of chromosome aberration have been detected in studies of human mesothelioma [9–11]. No specific chromosomal aberration has as yet

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been identified. Partial or total loss, and structural changes of chromosome 1, and partial or total gain of chromosome 7 have been among the most frequent chromosomal aberrations in malignant pleural mesothelioma [10]. In the search for diagnostic markers, prognostic factors and the mechanisms of carcinogenesis in mesothelioma, we collected data between 1982 and 1989 from all newly-diagnosed mesothelioma patients in the catchment area of the Helsinki University Central Hospital. This takes in about 25% of the Finnish population. Apart from mineralogical analyses of lung tissue [12, 13], we performed cytogenetic studies on fresh tumour specimens [9, 10] and on established cell lines [14]; ploidy studies [15]; clinical therapy trials [16]; and studies of treatment complications [17].

In this report we correlate the results of a larger number of more painstaking quantitative and qualitative fibre analyses of lung tissue with the patients' clinical characteristics, and with chromosome abnormalities in the tumour cells. Detailed treatment results and ploidy findings are not included in this report.

MATERIAL AND METHODS

Patients

41 patients with mesothelioma were studied. The diagnoses had been confirmed by the Finnish and EORTC Mesothelioma Panels; in 22 cases the results of both the cytogenetic analyses and the lung fibre content analyses were available; in 14 only the cytogenetic results were available; and in 5 only the mineralogical results were available. The patients were grouped according to the quantity and type of mineral fibres found by analysis. This grouping then served as the reference for the clinical and cytogenetic correlations (Table 1).

Mineral fibre analysis

The lung tissue samples were obtained as biopsy specimens at thoracotomy or at autopsy, when samples were taken from predetermined sites. The methods used for lung tissue sampling and preparation, as well as for fibre counting and identification, have been described [12].

Fibres were counted both by scanning (SEM) and transmission (TEM) electron microscope and the fibres were identified using X-ray microanalysis. Amosite and crocidolite are difficult to differentiate because they have almost identical X-ray spectra. Fibres showing only the silicon peak were classified as miscellaneous silicates. The data obtained from the fibre analyses were used to group the patients according to the quantity and the type of mineral fibres: group I $\geq$ 50% crocidolite/amosite (15 patients), group II $\geq$ 50% anthophyllite (4 patients), and group III $\geq$ 50% other fibre types (8 patients) (Table 1). A fourth group of 14 patients, for whom cytogenetic and clinical characteristics were available, but not mineral fibre analyses, is also included in Table 1.

Cytogenetic studies

Part of the cytogenetic data used in this study has been previously reported [9, 10]. To summarise, mesothelioma cells for karyotype analysis were obtained from 36 patients. Fresh tumour and pleural effusion specimens were obtained from 21 patients, tumour specimens only from 9 patients and pleural effusion specimens only from 6 patients. Samples were available before cytotoxic treatment from 29 patients. Metaphases were obtained from 32 patients, of whom 25 showed clonal chromosome abnormalities (19 of them before any treatment). The overall pattern of the cytogenetic findings was chaotic and heterogeneous: no chromosome change specific to mesothelioma was detected. The most frequent chromosome abnormalities in order of decreasing frequency were: −22 (44%), +7 (41%), −1 (38%), −3 (38%), −9 (34%), +11 (34%) and −14 (31%). (+/− denoting partial or total gain or loss). Translocations and deletions involving a breakpoint at 1p11–p22 were the most frequently occurring structural aberrations (34%). The chromosomal findings evaluated for correlation with the asbestos fibre data and patient characteristics were the presence of clonal abnormalities, non-clonal abnormalities and normal karyotypes, and the following specific chromosome abnormalities: −1, breakpoint at 1p11–p22, −3, del (3p), −4, +5, +7, −9, +11, +12, −14, −15, −16, −18 and −22 (−/+ denoting partial gain or loss of chromosomal material). To make Table 1 clear, only the occurrence of the clonal abnormalities involving chromosomes 1, 7, 9 and 11 are listed patient by patient. The other findings have been included in the correlation calculations, but are only presented in detail in our previous report [10]. Southern blot analysis was performed on 23 primary tumour specimens of malignant pleural mesothelioma, which had been previously chromosomally characterised. Several polymorphic markers were used to find numerical abnormalities of chromosome 7. An imbalance between the copy numbers of the two homologues of chromosome 7 was detected in two cases (patients 5 and 36) in which no numerical abnormality had been detected in the previous chromosome study [19].

Statistical analysis

All statistical analyses were performed using the BMDP statistical software package. Groups were compared by the likelihood ratio χ^2 test or variance analysis. A logarithmic transformation was used, because the distribution of the fibre counts was markedly skewed. Survival curves were constructed by the product limit method; differences were analysed with the Mantel–Cox test.

RESULTS

35 of the patients were men and 6 were women. The median age was 57 years (range 39–83). Some details of the patients characteristics are presented in Table 1. Of the 6 women, 2 (33%) were less than 50 years old; all showed clinical stage [18] IIA or less; 3 (50%) had epithelial, 2 (33%) mixed and 1 (17%) fibromatous type tumours. The corresponding figures for the 35 male patients were 7 (20%) less than 50 years old; 28 (80%) showing clinical stage IIA or less; 15 (43%) with epithelial, 19 (54%) mixed and 1 (3%) fibromatous type tumours.

None of the 41 patients in this study refused treatment. 38 patients received diagnostic and/or debulking surgery as part of their treatment, 26 received additional chemotherapy and 23 hemithorax irradiation. Only 15 received all three treatment modalities sequentially.

Median survival rates were as follows: for all patients (n = 41) 12 months (range 1–49); for the female population (n = 6) 25 months (range 7–49), one alive 74 months after diagnosis; for the male patients (n = 35) 8 months (range 1–33), one alive 42 months after diagnosis; for the patients aged 50 years or less (n = 10) 20 months (range 2–49); and for those with epithelial type tumours (n = 18) 7 months (range 1–49). Women lived longer than men after diagnosis (P = 0.0019) (Fig. 1). The association between clinical characteristics and both fibre analy-

Table 1. Patient characteristics, fibre concentration, main fibre type and main cytogenetic findings in 41 patients with malignant mesothelioma

No.*	Age	Sex	Stage at diagnosis†	Histological subtype	Survival (months from diagnosis)	Lung tissue fibre content‡	Clonal chromosomal abnormalities§				
							−1	1p#	+7	−9	+11
Group I ≥ 50% crocidolite and/or amosite											
—	65	M	I	Epithelial	7	140	&	&	&	&	&
1	47	M	IIB	Epithelial	8	26	+	+	−	+	+
—	57	M	IIA	Mixed	4	1500	0	0	0	0	0
9	72	M	I	Mixed	19	21	+	−	+	−	+
—	44	M	Peritoneal	Epithelial	5	3000	0	0	0	0	0
12	55	M	IIA	Mixed	13	11	+	+	−	+	−
33	47	M	IIA	Mixed	14	76	−	−	+	−	+
13	59	M	IIA	Epithelial	27	370	+	+	−	+	−
14	52	M	I	Mixed	14	3.1	−	−	+	−	−
36	42	M	IV	Fibromatous	2	4.1	−	−	−[e]	−	−
20	39	M	IIA	Mixed	20	88	+	+	−	+	+
21	42	M	IIA	Mixed	18	11	+	−	+	+	−
23	52	M	I	Mixed	14	13	+	−	+	+	+
25	71	M	IIA	Mixed	6	17	+	+	−	+	−
32	55	M	IIA	Epithelial	6	160	+	+	−	+	+
Group II ≥ 50% anthophyllite											
7	43	F	IIA	Epithelial	42	0.4	&	&	&	&	&
31	60	M	IIIB	Mixed	26	0.2	−	−	−	−	−
—	70	M	I	Mixed	18	1.2	0	0	0	0	0
38	57	F	IIA	Mixed	13	0.1	−	−	−	−	−
Group III ≥ 50% others											
—	64	M	IIA	Mixed	7	0.5	0	0	0	0	0
34	66	M	IIA	Mixed	42+	0.8	−	−	−	−	−
26	59	M	IIA	Mixed	5	5.5	−	−	+	+	+
35	71	M	IIA	Epithelial	17	1.2	−	−	−	−	−
—	50	M	IIA	Epithelial	1	0.4	−	+	+	+	+
37	54	M	IIB	Mixed	6	6.2	&	&	&	&	&
—	51	M	IIA	Epithelial	4	0.5	−	−	−	−	−
—	63	M	IIA	Mixed	33	< 0.1	0	0	0	0	0
Group IV fibre analysis not done											
2	44	M	IIIA	Epithelial	31	N.D.	−	−	−	−	−
3	42	F	IIA	Epithelial	49	N.D.	+	+	−	+	−
5	51	M	IIIB	Epithelial	3	N.D.	−	+	−[e]	−	−
6	75	M	IIA	Epithelial	3	N.D.	−	+	+	−	−
8	60	M	IIA	Mixed	6	N.D.	−	−	+	−	+
10	58	M	IIA	Epithelial	12	N.D.	−	+	+	−	+
16	83	F	I	Fibromatous	25	N.D.	−	−	+	−	−
18	67	M	IIA	Mixed	4	N.D.	+	−	+	−	−
19	55	F	I	Mixed	72+	N.D.	−	−	−	−	−
22	71	F	IIA	Epithelial	7	N.D.	−	−	−	−	−
24	51	M	IIA	Epithelial	5	N.D.	−	−	−	−	−
27	69	M	IIA	Epithelial	13	N.D.	+	−	−	−	−
28	73	M	IIA	Epithelial	14	N.D.	&	&	&	&	&
29	59	M	IIA	Mixed	4	N.D.	−	−	+	−	+

* Patient number is the same as in Tiainen *et al.* 1989 [10].

† Stage modified by Butchart staging system [18].

‡ × 10^6 per g of dried lung tissue measured by scanning electron microscope, N.D. = not done.

§ −1 = total or partial monosomy of chromosome 1, 1p# = breakpoint 1p11–p22, +7 = total or partial polysomy of chromosome 7, −9 = total or partial monosomy of chromosome 9, +11 = total or partial polysomy of chromosome 11. + = present, − = absent, & = analysis performed, no clonal chromosomal abnormalities, 0 = analysis not performed.

[e] No numerical clonal abnormalities in karyotype analysis, but gain or loss of chromosome 7 in the Southern blot analysis.

Cytogenetic findings after chemotherapy or radiotherapy in patient Nos. 2, 3, 5, 14, 20, 23 and 27.

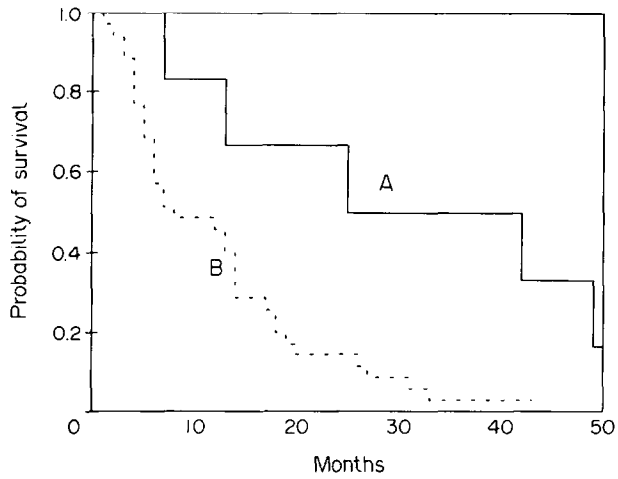

Fig. 1. Gender and survival (A = women, B = men, $P = 0.0019$).

sis and cytogenetic abnormality is shown in Table 2. Age, clinical stage at diagnosis, histological subtype, smoking history and performance status showed no statistically significant correlation with fibre concentration, main fibre type or chromosomal abnormality. Female gender showed a correlation with very low ($< 0.5 \times 10^6$ fibres per g dried tissue) fibre concentration ($P = 0.022$), and women had anthophyllite as the main fibre type ($P = 0.013$); but there was no correlation between female gender and specific chromsomal alterations. Dyspnoea, as the first symptom at the time of diagnosis, was associated with the low fibre counts ($P = 0.0372$) and was observed in 9/12 patients in the anthophyllite and 'other' main fibre type groups, whereas the absence of dyspnoea at diagnosis was observed in 10/14 patients in the crocidolite/amosite main fibre type group ($P = 0.039$).

High total fibre concentration matched well with crocidolite/amosite as the main fibre type (Table 3). All patients with low fibre concentration ($< 1 \times 10^6$ fibres per g dried lung tissue) were from the anthophyllite or 'other' groups ($P < 0.0001$). High fibre concentration also showed a correlation with partial or total loss of chromosome 1 ($P = 0.0005$), chromosome 4 ($P = 0.0069$), chromosome 9 ($P = 0.0201$) and chromosomal rearrangements involving a breakpoint at 1p11–p22 ($P = 0.0388$), as shown in Table 4.

The crocidolite/amosite fibre type was consistently accompanied by partial or total loss of chromosome 1 ($P = 0.017$), chromosome 3 ($P = 0.0322$), chromosome 4 ($P = 0.0345$) and chromosomal rearrangements involving del (3p) ($P = 0.0207$) (Table 5).

Survival curves analysed with the Mantel–Cox test showed the relationship between survival and lung tissue fibre concentration (Fig. 2), and between survival and fibre type (Fig. 3). Survival was better for patients with low fibre concentration ($< 1 \times 10^6$ fibres per g dried lung tissue) than for those with high lung tissue fibre concentrations ($P = 0.031$). Patients with crocidolite/amosite as the main fibre type had the worst prognosis, and those with anthophyllite the best ($P = 0.021$). The presence of chromosome 7 polysomy from the cytogenetic analyses, and the gain or loss of chromosome 7 in the Southern blot analyses, also showed a significant association with poor prognosis ($P = 0.038$) (Fig. 4).

Table 3. Fibre concentration and main fibre types in 27 patients with malignant pleural mesothelioma

Fibres × 10^6 per g dry lung tissue	Patients No.	%	No. of patients with ≥ 50% cr/am	≥ 50% chrys	≥ 50% ant	≥ 50% other
≥ 1000	2	7	2	—	—	—
999–100	3	11	3	—	—	—
99–10	8	30	8	—	—	—
9–1	6	22	2	1	1	2
< 1	8	20	—	—	3	5
Total ≥ 1	19	70	15	1	1	2
Total < 1	8	30	—	—	3	5

Table 2. The association between lung tissue fibre concentration, main fibre type, clonal chromosomal abnormalities and clinical data

Clinical characteristics	Lung tissue fibre concentration	Main fibre type	Clonal chromosomal abnormalities
Gender	0.022*	0.013†	N.S.
First symptom at the time of diagnosis	0.0372‡	0.039§	N.S.
Clinical stage			
Age			
Smoking	N.S.	N.S.	N.S.
Performance status			
Histological subtype			

* Female gender and lung tissue fibre concentration < 0.5 fibres × 10^6 per g.
† Female gender and anthophyllite as the main fibre type.
‡ Dyspnoea as the first symptom and low lung tissue concentration.
§ Dyspnoea as the first symptom and anthophyllite or other as the main fibre type.

Table 4. The association between specific chromosomal alterations and fibre concentration. The fibre counts are expressed as medians (× 10^6 fibres per g dried tissue)

Site of chromosomal alteration	Median fibre count if chromosomal alteration is present or not present: Present	Not present	*P* value
Breakpoint 1p11–p22	26	5.5	0.0327*
Monosomy 1	21	1.2	0.0005*
Monosomy 3	17	13	0.2996
Monosomy 4	26	5.5	0.0069*
Monosomy 9	17	3.1	0.0201*
Monosomy 14	26	11	0.0908
Monosomy 22	11	21	0.9424
Polysomy 7	11	11	0.0728
Polysomy 11	26	4.1	0.0760
Polysomy 12	26	11	0.8290
Trisomy 5	13	17	0.8994
del (3p)	17	13	0.8423

* Statistically significant.

Table 5. The association between specific chromosomal alterations and crocidolite and/or amosite as the main fibre type

Chromosomal alteration site	*P* value
Breakpoint 1p11–p22	0.1856
Monosomy 1	0.0017*
Monosomy 3	0.0322*
Monosomy 9	0.1176
Monosomy 14	0.6624
Monosomy 22	0.1481
Polysomy 7	0.4164
Polysomy 11	0.2868
Polysomy 12	0.1997
Monosomy 4	0.0345*
Trisomy 5	0.5843
del (3p)	0.0207*

* Statistically significant.

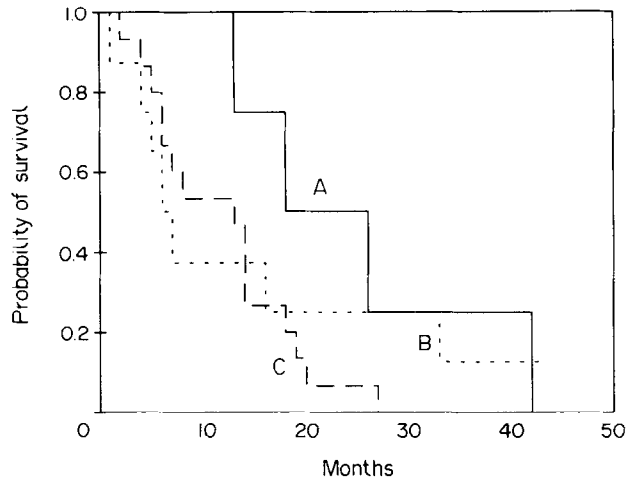

Fig. 3. Main fibre type and survival (A = anthophyllite, B = others, C = crocidolite/amosite, $P = 0.021$).

DISCUSSION

This paper coordinates material from clinical, mineralogical and cytogenetic studies which were performed prospectively on patients with malignant pleural mesothelioma. The material is unique in that the clinical studies and many of the experimental studies were performed prospectively and at the same institution; and in that the histological diagnosis had to be confirmed by two expert pathology panels.

Mineralogical fibre analyses were performed on only 2 out of the 6 women in this study of 41 selected patients; both had a low lung fibre burden and anthophyllite as the main fibre type. They presumably represent 'background' cases, which are not related to occupational exposure [12, 20].

Dyspnoea as the first symptom at the time of diagnosis was connected in a statistically significant manner with low lung tissue fibre count, and occurred more often in patients in the anthophyllite and 'other' main fibre groups. The importance of this correlation remains unclear, but may indicate less aggressive tumour behaviour. Prognosis for patients in the anthophyllite and 'other' groups was significantly better than for those in the crocidolite/amosite group. However, no correlation could be shown between the symptom at the time of diagnosis and prognosis.

A lung fibre concentration of more than 1 million fibres per g dried lung tissue, as measured by SEM indicates occupational exposure [21]. By this criterion, the lung fibre counts of our patients indicated occupational exposure in 70% of the cases, the median lung fibre concentration being 6.2×10^6 fibres per g dried lung tissue.

The relative pathogenicity of the different fibre types is widely debated: it is a central issue in legislation and in the development of public policy on occupational exposure to carcinogens.

Crocidolite and amosite are invariably associated with the development of mesothelioma in various occupational groups [22]. In our investigation of fibre concentration and main fibre type in the 27 patients in our study for whom mineral fibre analyses were available, crocidolite and/or amosite were the dominant fibres in 15/27 cases (56%). 13 of these 15 patients (87%) also had lung fibre concentrations over 10^6 fibres per g dried lung tissue.

Amphiboles (i.e. all the forms of asbestos other than chrysotile) accumulate in the lungs in increasing concentrations

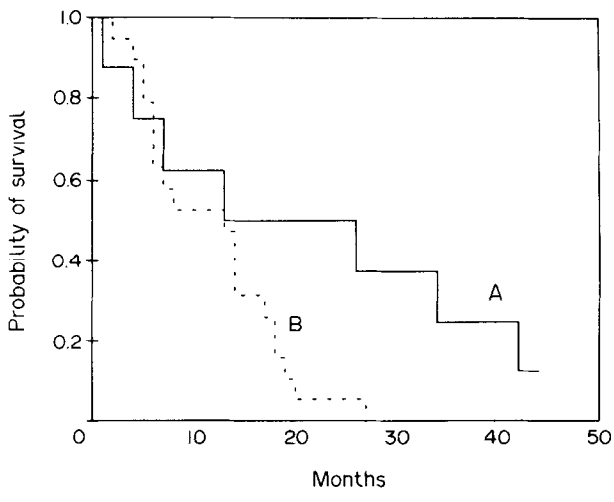

Fig. 2. Lung tissue fibre concentration and survival (A < 1×10^6 fibres per g, B ≥ 1×10^6 fibres per g, $P = 0.031$).

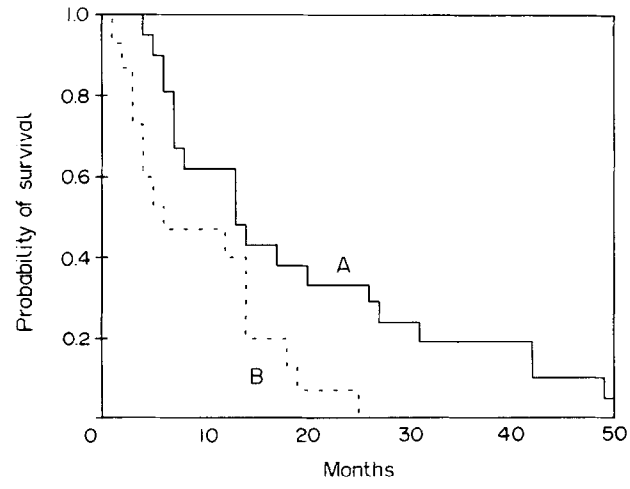

Fig. 4. Chromosome 7 polysomy and/or gain or loss of chromosome 7 in Southern blot analysis and survival (A = normal chromosome 7, B = abnormal chromosome 7, $P = 0.038$).

during the lifetime [23]; but chrysotile appears to reach a static concentration in which intake and removal are balanced. Therefore, a low chrysotile count does not necessarily imply the absence of past exposure [24]. From our mineralogical fibre analyses, 3/27 patients (11%) had chrysotile in their lungs; but in only one case did chrysotile make up 50% or more of the total fibre burden.

The only deposits of anthophyllite of commercial significance are in the USA and Finland. Previously reported mortality studies of Finnish asbestos miners have not indicated anthophyllite as a cause of mesothelioma [7, 25, 26]. Tuomi *et al.* [12] have recently analysed the mineral fibres in the lung tissue of 19 of the patients included in this study and of 15 randomly-selected autopsy cases. They found that anthophyllite was the most common amphibole in the reference group and that anthophyllite fibres were found in 70% of the mesothelioma cases. The study was nevertheless inconclusive as to the carcinogenic role of anthophyllite because there was no case reported involving exposure to anthophyllite alone. In the present study of patients with malignant mesothelioma, anthophyllite was found in 12/27 cases (44%) and, in contrast to previous studies, 4 patients showed exposure mainly to anthophyllite. The fibre concentrations in the lungs of these 4 patients were 1.2, 0.4, 0.2 and 0.1×10^6 fibres per g dried lung tissue. This would seem to indicate that there is indeed a carcinogenic role for anthophyllite.

We have reported previously a clear association between high total fibre burden (> 5 million fibres per g dried lung tissue), and partial or total loss of chromosomes 1 and 4 and chromosomal rearrangements involving a breakpoint at 1p11–p22 [10]. In this study we confirmed our previous findings and we also found a correlation between high total fibre concentration (≥ 1 million fibres per g of dried lung tissue), and partial or total loss of chromosome 9. In addition, we found that crocidolite/amosite as the main fibre type was accompanied by partial or total loss of chromosomes 1, 3, 4 and chromosomal rearrangements involving del (3p).

The mechanisms by which asbestos fibres cause mesothelioma remain unclear [27]. Lechner *et al.* showed in *in vitro* studies that asbestos fibres penetrate human mesodermal cells and induced multiple chromosomal breaks and rearrangements [8], which could lead to malignant transformation. Our findings could support this hypothesis, but of course we studied cells which were already malignant.

In the literature, prognostic factors for mesothelioma have been defined as histological subtype, gender, age and clinical stage of disease [28, 29]. We have previously reported chromosome 7 status [10] and the size of the S-phase fraction as analysed by flow cytometry [15] as additional prognostic factors in mesothelioma. In this analysis we found female gender, low total fibre concentration, anthophyllite as the main fibre type and normal chromosome 7 to be positive prognostic factors. There is evidence of a better prognosis for patients with pleural mesothelioma but without known asbestos exposure [29, 30]. With the availability of individual asbestos exposure information, we have also shown a clear correlation between high total fibre concentration and poor prognosis as well as between crocidolite/amosite as the main fibre type and poor prognosis.

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Reducing the Toxicity of the Combined Modality Therapy of Favourable Stage Hodgkin's Disease

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INTRODUCTION

FAVORABLE STAGE or limited extent Hodgkin's disease is highly curable. Depending on the age of the patient, if combined modality therapy (both radiation and chemotherapy) is employed, 90% or more of patients can be cured of the disease. Even with less favourable settings, combined modality therapy can eliminate the disease in approximately 75% of patients. Achievement of these excellent results, however, requires the use of detailed diagnostic or staging methods and maximal treatment programs. These methods are associated with considerable acute toxicity and morbidity and serious long-term morbidity and mortality. The succcessful treatment of patients with Hodgkin's disease 20 or more years ago has allowed us to recognise and quantify the serious and sometimes fatal treatment complications. The challenge that faces the clinical investigator of Hodgkin's disease today, is to reduce or eliminate the most serious acute and late management toxicities, without sacrificing the excellent curative treatment results which are now possible.

The major problems

The most serious acute and long-term toxicities for patients with favorable stage Hodgkin's disease that might be reduced or avoided are (*potentially fatal) staging exploratory laparotomy*, the asplenic state, surgical or radiation induced*, the severe and repetitive nausea and vomiting of chemotherapy, radiation induced abnormalities of bone and muscle growth and development, radiation pneumonitis and carditis*, chemotherapy and/or radiation induced sterility, chemotherapy induced secondary acute leukemia*, radiation induced secondary cancers*, radiation induced coronary artery disease*, prolonged treatment programs (6 months or longer).

Combined modality therapy

The use of both radiation and chemotherapy for the primary management of patients with Hodgkin's disease is controversial. Very few properly randomised studies can demonstrate a long term survival advantage resulting from the use of both modalities in primary management. This is because patients who are carefully staged and treated with radiation alone can be successfully treated with combination chemotherapy if they develop relapse of their disease. Slight survival advantages of combined modality therapy are diminished or erased by treatment-related deaths, more frequent after utilising maximal combined modality therapy [1].

This is not the situation for children, however, and lessons in treating adults can be learned from the treatment results and protocols for treating children. Because of the bone and growth development abnormalities of full dose irradiation of children, reduced radiation doses and fields are employed, and combination chemotherapy is always used. In some centers, staging laparotomy with splenectomy is avoided because adequate chemotherapy for occult disease is routinely utilized. At Stanford, children are currently clinically staged and treated with combination chemotherapy, with reduced cumulative doses of the major toxic drugs [three cycles of mustine, vincristine, procarbazine and prednisolone (MOPP) and three cycles of ABVD] to minimise the long-term risks of secondary AML, sterility and late cardiopulmonary toxicity of ABVD. The results have been excellent [2].

The Stanford approach for adults has been different. A relatively mild combination chemotherapy regimen has been devised, VBM (vinblastine, bleomycin and methotrexate) and used in combination with limited irradiation fields [3]. The VBM is well tolerated, acutely, with very little nausea, vomiting or hair loss, does not induce male or female sterility, and theoretically, should not induce secondary leukemia. The success of this management approach for laparotomy staged patients has lead to its evaluation for clinically staged patients. The results, to date, are very early but also encouraging. It would appear that maximal chemotherapy programs, associated with severe acute toxicity, sterility, secondary acute leukemia, and cardiomyopathy are not necessary to control minimal or occult Hodgkin's disease.

The goal of reducing long term serious morbidity is also appropriate for patients with more advanced and unfavourable Hodgkin's disease. A 12-week, dose-intensive regimen (Stanford

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