MESSAGE FROM THE PRESIDENT

I am honored being elected President of IMIG for the period 1997-1999. Gratitude should be expressed to two people, who contributed enormously to the organization of IMIG. Philippe Chahinian, my predecessor, has done a lot of work in the organization of the last IMIG meeting in Philadelphia. Brenda Gerwin has been the treasurer of IMIG since its foundation in 1991 and was active in the organization of the IMIG meetings in the USA. Per-Fredrik Ekhold, for several years a member of the IMIG committee, will follow up Brenda as Treasurer. The new Secretary of IMIG will be Steven Mutsaers, an active participant of the IMIG meetings for many years. Furthermore, I am happy to announce that three members of IMIG have accepted the invitation to join the IMIG Committee: Karin Mattson, Steven Albelda and Harvey Pass.

IMIG consists of an international group of scientists and medical practitioners interested in mesothelioma and asbestos induced changes in mesothelial cells. The aim of IMIG is to hold an International Mesothelioma Conference every two years, to facilitate the communication between the members and the sharing of resources. The summary of the last IMIG meeting held in May 1997 in Philadelphia is included in this newsletter. All the chairpersons of the various sessions are acknowledged for preparing the summaries.

The next IMIG meeting will be in 1999 in Europe. Two countries were considered and after exploration of the possibilities and discussion with the Committee we have decided to hold the next meeting 26th to 29th September 1999 in England, somewhere south of London. The Executive Committee of IMIG is glad to announce that this will be a joint meeting with a group of people interested in peritoneal healing. This group is having meetings on peritoneal healing and post-operative adhesion formation every two years. The IMIG meetings have a tremendous overlap with them in the field of mesothelial biology. This overlap will result in a broader scientific audience with different backgrounds, which is beneficial to IMIG. The program is not defined yet but there will be in addition to sessions on mesothelial biology specialized sessions on mesothelioma and post-operative adhesions. More news on this fifth IMIG meeting will be announced at the IMIG webpage and a flyer will be sent out via e-mail or post to all members on our mailing list 1998. This page is accessible by the following directory:
http://www.eur.nl/FGG/IMMU/meso.html

Looking forward to an inspiring meeting in 1999!

Marjan Verssel

IMIG mailing list

At the last IMIG meeting we asked the participants to fill in a form with personal information for the IMIG mailing list, unfortunately many people forgot it and a lot of forms were difficult to read. Therefore, we would like to ask you to send an e-mail to Steven Mutsaers with the following
information:
Title, Family Name, First Name, Male/Female, complete address including telephone, fax and most importantly e-mail address. We hope to forward future correspondence primarily through e-mail.

Report of 4th International Mesothelioma Interest Group meeting
Philadelphia, USA, May 13 to 15, 1997

Biology / Carcinogenesis
B. Gerwins (Bethesda, USA) and M.-C. Jaurand (Creteil, France)
Dr. Faux (Burlington, USA) presented work on the role of \([Ca^{2+}]_{in}\) and \([Ca^{2+}]_{ex}\) in the asbestos-induced protracted rise in c-fos and transcription factors observed in rat pleural mesothelial cells (RPMC). The experiments measured the transcription factor elevation in response either to crocidolite treatment or to \(H_2O_2\) by Northern blot or gel shift assays and tested modulation of these responses by treatment of RPMC prior to asbestos or \(H_2O_2\) treatment with the \([Ca^{2+}]_{in}\) chelator, Quin-2, or the \([Ca^{2+}]_{ex}\) chelator, BAPTA. The increase in DNA-binding by AP-1 and CREB after crocidolite treatment was inhibited by pretreatment with BAPTA but not with Quin-2. In the same cells, thapsigargin, which mobilizes \([Ca^{2+}]_{in}\), does induce the c-fos message and this is blocked by Quin-2 showing that Quin-2 can function in this cell type. In fact, crocidolite and thapsigargin synergize in c-fos induction, suggesting that they act by different mechanisms to produce the same result. In contrast, the increase in DNA-binding by AP-1 and CREB after \(H_2O_2\) treatment was inhibited by pretreatment with Quin-2 but not with BAPTA, suggesting that the fiber effects are distinct from the effects of oxidative stress generated by \(H_2O_2\) treatment. It was suggested that the entrance of \(Ca^{2+}\) into cells is important for the crocidolite response.

Dr. Ferriola (Research Triangle Park, USA) presented a study which investigated the levels of the apoptotic pathway regulators in the Bcl2 family in RPMC and the effect of amosite treatment on steady state RNA levels of these regulators. Dr. Ferriola reported that RPMC express the pro-apoptosis factors, Bax and Bclxs as well as the anti-apoptosis factors, Bcl2 and Bclxl. Since growth factors can affect the splicing patterns of the Bcl family genes, a line of RPMC, SFM1, was adapted for serum-free growth and treated with fibrous amosite or particulate grunerite. It was found that neiter Bcl2 nor Bax were significantly altered by fiber treatment. However, it was shown that, at 24 hrs post-amosite treatment a dose-dependent increase in Bclxl was demonstratable. Dr. Ferriola suggested that RPMC may show a decreased apoptotic response relative to other cell types as a result of this induction.

As background for his investigation, Dr. Mutsaers (London, UK) reviewed the secretion by mesotheliomas of an extensive ECM containing predominantly collagens types I and III. It is known, in other systems, that procollagen production can be stimulated by TGF-\(\beta_1\) and it has been demonstrated that TGF-\(\beta_1\) is mitogenic for mesothelial cells. Furthermore, it has been shown that cultured mesotheliomas produce TGF-\(\beta_1\) and that TGF-\(\beta_1\) activity is present in malignant effusions. Production of procollagen in response to TGF-\(\beta_1\) was measured in murine mesothelioma cell lines and in normal murine mesothelial cells. In normal cells, maximal stimulation was achieved at 0.4pM TGF-\(\beta_1\) whereas in mesothelioma cell lines, the maximally stimulatory dose was 40 pM. The levels of production achieved by stimulated normal cells never exceeded the basal levels of the mesothelioma cell lines, suggesting that the tumor cell lines might be already responding to endogenously produced growth factor and showed stimulation only at very high doses of exogenous factor. In order to test the hypothesis that ECM production effects mesothelioma growth, preliminary studies were conducted to determine if substitution of the proline analogue, thiaproline in culture medium could block production of stable collagen. At optimal doses of thiaproline, basal and TGF-\(\beta_1\) stimulated procollagen levels were reduced by approximately 50% and 70% respectively in normal and mesothelioma cells.
Dr. Prins (Rotterdam, The Netherlands) reported on his studies to delineate the transcriptional factors involved in the observed increase in transcriptional activity of the PDGF B-chain gene in MM. The PDGF B-chain promoter to -16kb from the transcriptional start site was analysed for Dnase hypersensitive sites. These were identified at -10kb, -7kb, -4kb and -2kb. Dr. Prins reported that a region from -65 to -61 represented the basal promoter and was occupied by nuclear factors both in MM and normal cells. However, gel shift assays indicated a quantitative difference, with higher concentrations of factors inducing gel shift in the MM cells. Specific binding factors were not identified. A region mediating transcriptional enhancement was identified at -9.9 kb in MM but this region was not active in normal mesothelial cells. Gel shift and Dnase footprinting assays delineated an area of 100 bp containing at least two sites separated by 20bp to which nuclear factors bound. Normal mesothelial cells contained factors binding to one of these sites while MM cells contained factors binding to both sites. Interestingly, binding of the second factor occurred only if the first site was occupied. The identity of the proteins involved in this complex is under further investigation. A report of this work appeared in the December, 1996 Biochimica Biophysica Acta.

Dr. Kumar-Singh (Antwerp, Belgium) presented a poster on overexpression of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) by malignant mesothelioma cell lines. Concentrations of VEGF and bFGF in medium conditioned for 72 hrs after seeding 10^6 cells was measured by ELISA assays. The cells compared were 4 malignant mesothelioma (MM) lines, 2 normal fibroblast (NF) cell strains and 1 normal mesothelial (NM) strain. Growth medium contained 10% FCS and was used as a negative control. Values reported were:

<table>
<thead>
<tr>
<th>Cell type</th>
<th>VEGF</th>
<th>bFGF</th>
</tr>
</thead>
<tbody>
<tr>
<td>serum control</td>
<td>&lt;5 pg/ml</td>
<td>&lt;5 pg/ml</td>
</tr>
<tr>
<td>NM (1)</td>
<td>&lt;5 pg/ml</td>
<td>&lt;5 pg/ml</td>
</tr>
<tr>
<td>NF (2)</td>
<td>206 pg/ml</td>
<td>18 pg/ml</td>
</tr>
<tr>
<td>MM (4)</td>
<td>&gt;1000 pg/ml</td>
<td>&gt;32 pg/ml</td>
</tr>
</tbody>
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Dr. Kumar-Singh (Antwerp, Belgium) presented a poster on the prognostic value of basic fibroblast growth factor (bFGF) in malignant mesothelioma. This study reports the results of immunostaining tissue sections of 20 malignant mesotheliomas (MM) and 15 non-neoplastic mesothelia (NM) for bFGF. Reactivity was scored as intense, moderate or negative. Clinical histories indicated that cases with intense staining had shorter survival than those with moderate or negative staining.

<table>
<thead>
<tr>
<th>Sample (nr)</th>
<th>Intense</th>
<th>Moderate</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>MM (20)</td>
<td>17</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>NM (15)</td>
<td>0</td>
<td>6</td>
<td>9</td>
</tr>
</tbody>
</table>

One poster by K. Takabe et al. (Kanagawa, Japan) reported on mineral fiber content in pleural plaques of patients with malignant mesothelioma (MM). Asbestos bodies and fiber counts were compared to those obtained in autopsy subjects with pleural plaques. The results confirmed the expected greater amount of asbestos bodies in the lung and pleural plaques of patients with MM. The number of fibers > 5 μm of length was also greater in patients with MM than in subjects with pleural plaques. Moreover, the aspect ratio of fibers found in pleural plaques of subjects with MM was significantly higher than that of subjects with pleural plaques. This difference was not observed in the lung. The results reported by Takabe et al. suggest the importance of fiber geometry in pleural pathogenesis.

The abstract of Buard et al. (Creteil, France) could have been included in the Therapeutics or Immunology sessions. In order to better understand the mechanisms by which cytokines could directly affect the proliferation of mesothelioma cells, IFNγ signal transduction pathway has been studied by Buard et al. in several mesothelioma cell lines. The IFNγ signaling pathway was rapidly activated upon treatment with IFNγ. The lack of response of certain mesothelioma cell lines was related to a defect in expression and/or activation of JAK2 and SAT1.

Pleural effusions and serum in patients with MM have been studied by Hervé et al. (Creteil, France) in order to characterise α1-acid glycoprotein (AAG), a protein of the
acute phase reaction, on the basis of its polymorphism and genetic variants. Three main AAG phenotypes can be found in the human population, namely F1S/A, F1/A and S/A. In MM the frequency of the phenotypes were different from that of control patients and the relative proportions of F1 and/or S variants was enhanced. Moreover the AAG microheterogeneity pattern in MM was also different as determined by electrophoresis indicating changes in concentration and glycosylaion.

Drs. Warn (Norwich, UK), Mutsaers (London, UK) and Harvey (Norwich, UK) reported on the role of Hepatocyte Growth Factor/Scattering Factor (HGF/SF) in migration and proliferation of mesothelial and mesothelioma cells. HGF/SF is produced and secreted by both normal and mesothelioma cells (Mutsaers et al., Harvey et al.). HGF/SF may have an autocrine action since the c-met receptor is also found in mesothelioma cells (Mutsaers et al., Harvey et al.). HGF/SF was shown to induce morphological changes and increased cell motility in these cells suggesting a possible role in tumor migration and invasion (Warn et al.).

Immunology

B.W.S. Robinson (Perth, Australia)

There continues to be substantial interest in the immunology of mesothelioma, including development of potential immunotherapies. Cantinschi (Perth, Australia) demonstrated that systemic administration of the cytokine IL-12 in a murine model of mesothelioma prevented growth of the tumour. She then used IL-12 gene transfection technology and showed that this molecule, if produced by tumour cells, prevents tumour growth. The effects of IL-12 in the system correlated closely with the degree of T cell infiltration. Importantly, mixing IL-12-producing tumour cells with wild-type tumour cells showed that high efficiency gene transfer would be required (e.g. around 80%) before limitation of tumour growth could be anticipated. Kang (Philadelphia, USA) studied a variety of immunological parameters in patients with mesothelioma. No correlation between stage of disease and immune responsiveness was observed. Both cellular and humoral immune responses to adenoviruses were evaluated in patients with all 4 stages of disease in this study. Gelfand (Philadelphia, USA) sought to determine whether adenoviral gene therapy induced TH1 or TH2 phenotype by evaluating IL-4 or IFN-γ production. Both the amount of IFN-γ produced and the number of cells producing it increased 20-fold compared to IL-4 following exposure to adenovirus, suggesting that intrapleural adenovirus induced a TH1 response. Marzo (Perth, Australia) utilised antisense oligonucleotide technology to block the mesothelioma-derived production of TGF-β in vivo. She showed that antisense blockade of TGF-β2 in vivo markedly diminished tumour growth, although the effect appeared to be a direct anti-proliferative effect rather than an immune enhancing effect at this stage. Mutti (Verona, Italy) utilised mesothelioma cell lines and showed that they could present recall antigens in vitro to autologous blood CD4+ lymphocytes, suggesting a potential role for these cells in the stimulation of at least a recall CD4, class II-restricted response in vivo. Porter (Verona, Italy) used mesothelioma cell lines and demonstrated that IL-2 can be directly modulatory of their growth. All 4 mesothelioma cell lines studied expressed IL-2 receptors on the surface and IL-2 reduced cell growth, although at rather high concentrations (up to 3,006 IU).

Genetics/SV40

J.R. Testa (Philadelphia, USA) and M. Carbone (Chicago, USA)

The association of SV40 with human mesotheliomas and the possibility that SV40 may play a role in tumor development represented one of the hot topics of the meeting. SV40 is a DNA tumor virus that preferentially induces mesotheliomas when injected into hamsters. Humans were exposed to SV40 through contaminated Adeno and Polio vaccines administered between 1955 and 1965. Testa, (Philadelphia, USA) and Mutti (Verona, Italy) reported their independent preliminary findings confirming the presence of SV40-like sequences in many mesotheliomas. Linnainmaa (Helsinki, Finland) reported negative results for SV40 sequences in
Finnish mesotheliomas. She indicated that Finland did not receive SV40-contaminated polio vaccines, and she suggested that this may account for her negative data. Giordano, (Philadelphia, USA) found SV40-like DNA sequences and SV40-Tag expression in human mesotheliomas. Giordano found that Tag was physically associated with the tumor suppressor genes RB1, RB2/p130 and p107, suggesting that the SV40 genome was biologically active. These results confirmed similar data presented by Carbone (Chicago, USA) indicating that SV40 Tag was associated with p53 in some of the mesotheliomas he studied. Both papers describing these findings appeared in the August issue of the journal Nature Medicine. Testa was asked to organize a consortium to blindly test a number of mesotheliomas to confirm the presence of SV40-like sequences in human mesotheliomas.

The Genetics session focused on the role of tumor suppressor genes and putative oncogenes in mesothelioma. Kane (Providence, USA) presented data demonstrating increased sensitivity to induction of mesotheliomas by crocidolite asbestos in transgenic mice homozygous or heterozygous for a disrupted p53 allele. Cheng (Philadelphia, USA) demonstrated that the neurofibromatosis type 2 gene, NF2, is mutated in many human mesotheliomas. Western blot analysis of mesothelioma cell lines revealed either no NF2 protein expression or protein of aberrant size in nearly 70% of cases, suggesting that these specimens have mutations resulting in truncation of NF2 protein or inframe deletions. These results indicate that NF2 alterations may play an important role in the development of mesothelioma and that NF2 could be a potential target for cancer therapy. Bell, also from Philadelphia, constructed a high resolution deletion map of chromosome arm 6q in human mesothelioma. Allelic losses from 6q were observed in more than 60% of the tumors she examined. At least three non-overlapping regions of 6q loss were identified, suggesting the existence of multiple tumor suppressor loci in 6q which may contribute to the pathogenesis of mesothelioma. Boylan (Charleston, USA) described three genes isolated by the

differential display technique that are upregulated in mesothelioma cell lines, and she proposed that these genes could play a role in the immortalization and/or transformation of mesothelial cells.

Pathology

A. Hjerpe (Huddinge, Sweden)

During the pathology symposium 7 papers were presented and discussed, focusing on diagnostic parameters such as basic morphology, immunocytochemical reaction patterns and the importance of hyaluronan production often seen in association with these tumors.

Flening (Baltimore, USA) presented a study of morphological and immunological findings, aiming at the distinction of desmoplastic mesotheliomas from chronic fibrosing pleuritis. Cytologically the mesothelioma diagnosis was favored by high cellularity, atypia and mitoses. Architecturally the tumors often showed storiform patterns with irregular organization of extracellular matrix components, while parallel collagen bundles and organized finer vessels indicate a benign fibrosis. Cytokeratin reactivity was more expressed in desmoplastic mesotheliomas than in the benign fibrosis of the pleura.

Three papers were presented, concerning immunocytochemical criteria for the distinction between (epithelial) mesothelioma and adenocarcinoma. In the first of these (Hjerpe) the covariation of the reaction patterns obtained with conventionally recommended and commercially available antibodies was studied. The analysis yielded a logistic regression model for the interpretation of a battery including 9 antibodies. As discussed from the floor, this model is preferably used in two steps with staining for CEA (DAKO MoAb) as the first and the remaining battery only for those negative to CEA.

Another difference between mesothelioma and adenocarcinoma is the differential expression of cadherins. Peralta Soler (Winnewood, USA) presented a paper on the differential diagnostic importance of assessing the expression of N- and E-cadherins. Using one
Epidemiology

B. Case (Westmount, Canada)

Studies were presented from Canada, Finland, the United States and Australia. Camus (Montreal, Canada) presented the means of derivation of an exposure model for women in the chrysotile mining regions of Quebec, Canada. Exposure was assessed for all women living in the area over age 30 in 1970-1989. Methods used included historical data on production, wind patterns, mine expansion, introduction dates of control technologies, and analysis of fiber samples which are now filtered out. Questionnaire data for women and air measurements in the area in more recent years were also used. Results were used to extrapolate risk estimates for lung cancer and mesothelioma using the linear model used by the U.S. Environmental Protection Agency and others. Average exposures, derived with the help of an expert panel, were extremely high, ranging from 74 to 125 fiber-years including a contribution from domestic or household exposure (which was present in 70% of women). Case (Montreal, Canada) showed comparisons between the extrapolated risk estimates and cases actually observed in (1) Quebec mortality records and (2) a case-finding study among Quebec women dying of mesothelioma 1970-1989. Deaths from pleural cancer (ICD9 163) were seven in this time period (30 per million vs. a background rate of 3 per million). Possible incident cases found in the mining area were 31. Twenty-four were in the relatively “high-tremolite” Thetford Mines region and 7 near the town of Asbestos. Seven incident cases (six in Thetford) were known to have occupational exposure; five were known to have household exposure. A preliminary review of pathology records suggests 12 cases are “definite” (corresponding to an incidence of 60 per million). Both mortality and incidence appear to be one order of magnitude above Quebec background rates and one order of magnitude below rates predicted by the linear model, based on the exposure estimates. Karjalainen (Helsinki, Finland) presented an overview of mesothelioma in Finland from 1960 to 1995, with an emphasis on the changes observed in the last ten years. Overall rates are lower than those observed in some other countries,

own and one commercially available antibody (against N- and E-cadherin, respectively) on clinical material, the former reacted in 12/13 mesotheliomas and the second in 13/14 adenocarcinomas and with no expression of both epitopes in the same case.

Betta (Allesandria, Italy) presented results with the AMAD-2 antibody and with antibodies to calretinin in malignant mesothelioma and in mesothelial hyperplasia. They were both found to be sensitive markers for mesothelial lineage, the latter mainly reacting in epithelially differentiated cells. It was mentioned that the epitope recognized by AMAD-2 is temperature sensitive, necessitating the use of low temperature paraffin during embedding.

Kitagawa (Toyama, Japan) presented results from the Japanese Mesothelioma Panel and the independent Osaka Mesothelioma Panel, two diagnostic panels that have been operating since 1973 and 1984, respectively. The diagnostic evaluations were based on routine and ancillary diagnostic techniques, including the analysis of hyaluronan contents in effusions. The importance of panel opinions was indicated.

Hyaluronan seems to be a molecule of so far unexplained importance for the mesothelioma cell. Heldin (Uppsala, Sweden) showed that in mesothelioma cell lines, themselves not expressing the hyaluronan synthase, there is a production of PDGF-BB which may cause paracrine stimulation to hyaluronan synthesis by surrounding mesenchymal cells. Furthermore, transformation of the mesothelial cell seemed associated with the upregulation of specific hyaluronan receptors.

In the final study of the Pathology session Roboz (New York, USA) presented data indicating that most of the serum hyaluronan was protein bound and inaccessible to reagents based on reactions with specific ligands (the Pharmacia kit). In samples from mesothelioma patients the obtained serum concentrations were of the same order as those found in the tumor effusions. The analysis was also used to monitor the enzymic degradation of hyaluronan.
due to a low rate of urbanization in the 1950's and early 1960's and the wide use of anthophyllite. Nonetheless, the same increasing incidence noted elsewhere is observed, with an overall age-adjusted rate of 10 per million in 1991. Female cases also showed a rise in recent years, with an apparent peak at four per million around 1986. There was a strong rural-urban gradient among men, with rates up to 20 per million in large cities, up to 10 per million in "new urban" centres and up to 5 per million in rural areas. The rate for males over 65 and for males over 75 is still increasing, but there is no increased incidence in lower age groups. Overall, the impression is more in line with recent observations in the U.S. (that incidence is peaking now or in the next decade) than the observations in the United Kingdom by Peto and others. An encouraging sign was the high rate of reporting of occupational mesothelioma: this increased from 11% of male pleural cases in 1984-85 to 90% in 1993-1995. Male peritoneal cases attributed to occupation have increased from zero to 50% in the same period. There were 30 male work-related cases 1993-95. Female cases remain largely non-occupational with 16% of pleural cases and no peritoneal cases attributed to job status in 1993-95. Ilgen (Bryn Mawr, USA) presented data concerning the Libby, Montana vermiculite mine in which high asbestiform tremolite content has been shown by two independent studies to produce risks for lung cancer and mesothelioma. While individual data on the deaths in this small cohort is scant, Dr. Ilgen believed the risk might have been overestimated due to a number of factors, including diagnostic misclassification and undocumented exposures to other carcinogens at the mine site. Dr. Ilgen also presented data on the chrysotile mine at Coalinga, California. Little individual data is available. There has been no epidemiological study of the 900 miners and millers at the site. Of 279 men in a Johns-Manville on-site plant there was follow-up only for 40 who had worked for 30 years. None had asbestos-related diseases. Similarly among 50 men who had x-rays none showed asbestos-related changes. However, morphometric analyses of rodents exposed to Coalinga chrysotile showed no significant increase in fibrosis or interstitial matrix volume at 24 months after exposure. (UICC-B and Jeffrey Mine chrysotile show marked increases in both parameters). Similarly, lung burden in rats showed no significant accumulation of fibers, while there were increases in both Canadian chrysotile samples. "Alveolar macrophage response" and numbers of tumors were reported to be very low in the California-chrysotile exposed rats, although these results (from the National Toxicology Program) have not been published. Musk reported (Perth, Australia) on incidence of malignant mesothelioma after both occupational and environmental exposures to Wittenoom crocidolite. Exposure patterns were generally of short duration due to the limited life of the mine and the extreme climatic conditions. Cohorts of 6910 former workers and 4598 ex-workers have been assembled. To date, 45 cases have been seen in residents and 200 in ex-workers. Residents are believed to have been exposed to levels of approximately 0.5 fibers/µl for varying duration, measured for the most part in months rather than years. Exposures were estimated in occupational groups using work histories, hygiene measurements and public records. Mesothelioma rates in both cohorts show a dose-response relationship, with the upper end of the line for residents below the lower end for occupational cases. Exposures were generally very high in cases. The reported range was 7 days at 20 fibers/µl to 10 years at 100 fibers/µl. In conditional logistic regression, the strongest factor was time from first exposure (in accordance with the models of Berry and Peto). However, both duration of exposure and exposure intensity had independent significant relation to incidence. The form of the dose-response curve was similar in both occupational and non-occupational cases. Case incidence is still increasing.

Clinical studies

P. Chahinian (New York, USA)
Several communications were presented by the following speakers. Corresponding abstracts are published in the appropriate sections. Knuuttila (Helsinki, Finland) discussed "Radiological evaluation criteria for
malignant pleural mesothelioma. Comparison of CT and MRI. This project is currently the subject of a prospective study by the authors using improved MRI imaging techniques with quick breath-holding sequences and intravenous contrast medium. Tammilehto (Helsinki, Finland) presented "Factors affecting surgical strategies in patients with malignant pleural mesothelioma". This was updated to include 148 patients. Survival was correlated with histologic type, performance status, and clinical stage. Radical surgery did not appear to alter the natural history of the disease. Baas (Amsterdam, The Netherlands) discussed "Photodynamic therapy with m-THPC as adjuvant treatment for resected malignant mesothelioma". Complications of this procedure were detailed and included possibly two cases of myocardial infarction. Robinson (Tampa, USA) presented "Induction chemotherapy in pleural mesothelioma precludes the technical performance of an extrapleural pneumonectomy". These authors observed loss of the usual extrapleural plane along the endothoraic fascia in 3 patients who received induction chemotherapy with cisplatin and doxorubicin before surgery. This effect apparently linked to chemotherapy prevented the safe performance of extrapleural pneumonectomy. Boutin (Marseille, France) summarized his latest chemotherapy trial in his communication "Malignant pleural mesothelioma. Results of a Phase II trial of combined chemotherapy". The chemotherapy was a combination of cisplatin, mitomycin, 5-fluorouracil, leucovorin, and etoposide (PMFE). Objective response rate was a respectable 34% among 50 evaluable patients, and more importantly the median survival was 16 months. The core of this regimen is based on the nude mouse studies conducted by Chahinian et al., showing efficacy of the cisplatin-mitomycin combination. Whether these results are superior to the cisplatin-mitomycin clinical results described by Chahinian and the Cancer and Leukemia Group B would require a prospective trial. Ruffi (Villejuif, France) presented his results of another drug combination, "Phase II study of paclitaxel (Taxol) and cisplatin in advanced pleural malignant mesothelioma". A response rate of only 6% (one partial response) among 17 patients was observed, although there were 11 stabilizations. More mature data are needed to assess survival. One possible explanation for the low objective response rate could be that selection criteria included patients with a minimum pleural thickness of 1 cm by CT scan, thereby excluding patients with early disease. This combination has been active in non-small cell lung cancer, however, and further trials are indicated in mesothelioma before firm conclusions can be made about its efficacy. Nakano (Hyogo, Japan) presented his experience with "A pilot Phase II study of irinotecan (CPT-11) in combination with cisplatin administered intravenously to patients with malignant mesothelioma". Dr. Nakano gave pharmacokinetic data of CPT-11 in the serum and pleural fluid of patients with pleural effusions and also made the interesting observation that the area under the curve of SN38 (a metabolite of CPT-11) is higher in patients with epithelial mesothelioma as compared to those with sarcomatous type. This is an important and new finding which should be considered when analyzing results of chemotherapy in mesothelioma. It is advisable to breakdown response rates by cell type. It is also well known that sarcomatous mesothelioma has a worse prognosis than the epithelial type. The response to the combination of CPT-11 and cisplatin included 3 partial ones among 11 patients (objective response rate of 27%), and also included one regression in a patient with evaluable disease (total response 4/11 or 36%). The activity of this regimen also deserves confirmation. Castagneto (Torino, Italy) concluded the oral presentations by presenting his trial "Intracavitary and systemic rIL-2 in the treatment of malignant pleural mesothelioma". Among 31 patients, response at the pleural effusion level was 90%. Measurable objective tumor response was 22.5%. Toxicity was moderate.

Several posters were also presented as part of the session on Clinical Studies. Zaccearia (Trieste, Italy) presented "Malignant pleural mesothelioma. Prognostic factors". This was a retrospective study on 181 patients, confirming the prognostic value of cell type, performance status, and stage. Tonomura (Hyogo, Japan) showed his experience with
"Immunotherapy using streptococcal preparation OK-432 for the treatment of malignant mesothelioma. A preliminary study". Five out of six patients had a response in term of control of pleural effusion. There was no objective tumor response, however. Mikulski (Bloomfield, USA) presented "The use of Onconase for patients with advanced malignant mesothelioma". Onconase is an RNase isolated from the eggs of the leopard frog and produced partial responses in 4/25 patients (16%), with a median survival of 10.1 months. A Phase III trial comparing Onconase to doxorubicin is planned for patients with mesothelioma. Lopez (Paris, France) presented a protocol "Local adoptive immunotherapy using IFNgamma-activated autologous macrophages in malignant pleural mesothelioma. A phase I/II study." Patients are treated with sequential intrapleural injection of autologous activated macrophages grown in vitro from blood monocytes and stimulated with IFN gamma. Linnainmaa (Helsinki, Finland) discussed "Individual variation in response to cytotstatic chemotherapy in the treatment of mesothelioma. In vitro studies in human cell lines." These authors evaluated the sensitivity of mesothelioma cell lines to gemcitabine or paclitaxel in correlation with deletions of the GSTM1 and NAT2 genes which are involved in drug detoxification.

Gene therapy
S.M. Albelda (Philadelphia, USA)
Cancer gene therapy is in its infancy and faces a number of current major limitations including lack of understanding of the genetic defects in most types of cancer (including mesothelioma) and the inability to introduce transgenes into most tumour cells. Despite these problems, mesothelioma is an attractive target because of its resistance to conventional therapy, its tendency to remain localized until late in the course of the disease, and the easy access to the chest cavity.
Two groups have reported results of Phase 1 gene therapy trials in humans. One group at the University of Western Australia, led by Robinson, is using immunotherapy with introduction of the interleukin-2 gene into tumours. The IL-2 cDNA has been introduced into a replication incompetent vaccinia virus that is being injected into subcutaneous nodules of patients with mesothelioma once every three weeks for a maximum of four cycles. At the time of IMIG, eight subjects had been studied. No transmission of vaccinia virus was noted and no other toxicity occurred. Transgene was detected by PCR reaction in some patients. Future plans include more frequent injections and the use of additional cytokines.
The other Phase I trial is being conducted at the University of Pennsylvania under the leadership of Drs. Steven Albeida and Larry Kaiser. This trial introduces an enzyme (the Herpes Simplex Thymidine Kinase gene that converts a prodrug (ganciclovir) into a "suicide gene") into the chest cavity of patients with mesothelioma using a replication adenovirus vector. A 15 patient Phase 1 dose-escalation trial has been completed. Minimal toxicities were noted, clear gene transfer into the superficial layer of tumour cells was seen, and strong immune responses to the adenovirus were detected. No clear cut anti-tumour effects were observed. Future plans include a Phase 2 trial of direct injection in patients with minimal disease and a second trial of gene therapy as adjuvant therapy to surgical debulking.
Although these trials are in very early stages, both groups are optimistic that gene therapy approaches will be an important weapon in the battle against mesothelioma.

Meetings
American Thoracic Society
ALA/ATS
April 24-29, 1998
Chicago, USA

European Congress of Oncology - Multimodality Treatment in Malignancies
September
Athens, Greece
Information: Amphitrión Congress Organizing Bureau, Athens, Greece, Tel.: 30 2 322 8884, Fax: 30 1 324 4158

European Respiratory Society
September 19-23, 1998
Geneva, Switzerland
7th International Symposium on Particle Toxology
October 10-13, 1999
Maastricht, The Netherlands

Meeting on current topics in inhalation toxicology including PM10, ultrafine particles, fibers, pulmonary inflammation and cancer. Target-audience: toxicologists, clinicians, epidemiologists.

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