Clinical trials in Mesothelioma: Australia

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Abstract:

Australia has one of the highest incidences of malignant mesothelioma in the developed world, due to asbestos mining and production, and occupational use of this fiber. Although the population of Australia is relatively small, health care resources are concentrated in the major capital cities, allowing tertiary referral centres to develop interest and expertise in rare tumours such as mesothelioma. Several Australian centres have active investigator-initiated clinical trial programs in this disease. Current research programs encompass the use of radiotherapy in mesothelioma, second line systemic therapy with novel agents, maintenance therapy after first-line treatment, and study of clinical trial endpoints and imaging in mesothelioma. The clinical trials currently underway in Australia are described and discussed.

Introduction:

The mineral resources of Australia include rich natural deposits of asbestos, which were mined for domestic use and export for over 100 years, between 1880 and 1983. Asbestos production increased over the first half of the 20th century, and crocidolite asbestos became the most important fiber mined with the opening of the Wittenoom mine in the north of Western Australia in 1937. Wittenoom closed in 1967, but mining of crocidolite asbestos continued at other sites, and chrysotile asbestos was mined until 1983[1]. The legacy of asbestos exposure amongst miners, mill-workers, wharf workers Wittenoom residents and their children remains (Figure 1), with one of the highest mesothelioma incidence rates in the world, almost 60 per million per year in males[1]. Whilst Western Australia has the highest incidence of mesothelioma in Australia (7.9 per 100,000 population in males), larger numbers arise in the eastern states of Australia, with their numerically larger populations (181 new cases in NSW in 2001, 4.8 per 100,000 in males). In 2001, there were 567 diagnoses of mesothelioma reported Australia-wide [2].

Healthcare delivery in Australia is concentrated in the state capitals in much of the country, with limited tertiary hospital care and oncology expertise in rural areas. This means that despite relatively small patient numbers, the majority of patients with mesothelioma can expect to be referred to a respiratory physician or medical oncologist with expertise and a large caseload of patients with mesothelioma. The availability of financial compensation for many Australian patients with malignant mesothelioma [3] is another reason why a relatively small number of physicians are involved with the management of this disease. This concentration of patients in relatively few centres around the country is clearly beneficial for the development of clinical trials at individual sites, and co-operatively Australia-wide.

Perth is the capital city of Western Australia with a population of approximately 1.5 million. It is the closest major city to the mining town of Wittenoom. There has been no asbestos mining in Wittenoom since 1967, and the population of that town has dwindled to a small number of people who choose to stay despite the known health risks. However, the population of often unskilled and itinerant workers with anywhere from a few weeks to a few years exposure to asbestos has spread throughout the state. Exposure in the building industry, dockyards, or Navy and merchant navy is also common in the Western Australian population. The majority of patients with mesothelioma are referred to clinician members of the Perth Mesothelioma Group, an informal consortium of clinicians and researchers predominantly based at Sir Charles Gairdner Hospital. This group is active in clinical and preclinical research in this disease. Previous clinical trials from this group include reports of the use of cisplatin and gemcitabine in mesothelioma [4, 5], and trials of immunotherapy, gene therapy, and chemo-immunotherapy approaches [6-9].

Co-operative group clinical trials in Mesothelioma in Australia:

The conduct and planning of clinical trials in mesothelioma in Australia will be greatly facilitated by the recent formation of the Australasian Lung cancer Trials Group (ALTG). The

inaugural meeting of the group was in Sydney in February 2004. Full membership is open to medical and non-medical persons active in and interested in the conduct of Australian clinical trials in lung cancer. The mission statement of the ALTG is to "reduce the incidence, morbidity and mortality of lung cancer in Australia and New Zealand through the co-ordination and facilitation of high quality clinical research". The group meets twice yearly for submission, scientific review and discussion of potential investigator-initiated projects and identification and formulation of important clinical research questions. The ALTG will also co-ordinate and develop accepted multi-centre trials, collaborate with national and international clinical trials groups, and give strategic assistance in obtaining funding. The objectives of the ALTG include improving patient access to clinical trials and educating patients with lung cancer and mesothelioma about the role of clinical trials in clinical care. This new group is likely to play an important role in clinical trials in mesothelioma in this region.

The discussion below covers current clinical trials and investigational approaches to the clinical management of mesothelioma in Australia.

Clinical trials of radiotherapy for mesothelioma in Australia

The role of radiotherapy in the management of mesothelioma in Australia has followed practices in the larger institutions in the United Kingdom and North America, as local clinicians adopted standards detailed in oncological textbooks, journals and conference presentations. Two reviews of the experience from the Peter MacCallum Cancer Institute in Melbourne during the 1980s reflect this approach [10, 11]. The majority of patients are treated with a palliative intent to small volumes over one or two weeks, without a coordinated plan involving the other specialties of surgery and medical oncology. No survival benefit was demonstrated for radical radiotherapy, but short courses produced useful palliation in occasional patients [12]. Standard treatment modalities included orthovoltage, megavoltage and electron beam radiotherapy, but in well-meaning attempts to enhance the poor responses from conventional radiotherapy, various innovative practices were evaluated, including moving strip radiotherapy, brachytherapy and UHF microwave radiation [13], without success.

In 1997 a randomised trial of prophylactic electron beam irradiation for thoracic drainage of thoracoscopy sites was initiated in Perth. No benefit was found for a single fraction of 10 Gy using 9 MeV electrons to 58 chest wall sites, with three subcutaneous masses in the control arm and two in the prophylactic radiotherapy arm [14].

In December 2002 Perth was host to the 6th International Mesothelioma Interest Group meeting, recognising the high incidence of the disease and research contributions from Australia. Following a presentation by Dr Craig Stevens, a radiation oncologist from the MD Anderson Cancer Center in Houston, Texas in which he described a novel radiotherapy technique using intensity modulated radiation therapy (I.M.R.T.) for postoperative treatment following extrapleural pneumonectomy (EPP) with excellent locoregional control, a new approach to managing mesothelioma patients was considered by staff at the Austin Hospital in Melbourne. Stevens reported on the radiosensitivity of mesothelioma cell-lines [15] and the importance of targeting a large volume including the full hemithorax after radical surgery, guided by close interaction with the surgical team to define the surgical bed and include the insertion of the diaphragm prior to resection and replacement by a synthetic membrane [16].

A pilot study was subsequently undertaken in Melbourne to treat regions of gross residual disease in patients who had undergone pleurectomy/decortication with phototherapy [17] using 3D-conformal radiotherapy to high doses, limited by the need to observe tolerances of adjacent normal organs including the intact ipsilateral lung. IMRT had been instituted for selected patients with prostate and head and neck cancers at a few radiation oncology centres in Victoria and New South Wales, but with the much larger target volumes and complexity involved in limiting the dosage to multiple adjacent organs for treating mesothelioma cases, available resources necessitated preliminary development at a single Australian centre. The Austin

Hospital had the advantages of a dedicated team of thoracic surgeons committed to the multidisciplinary management of thoracic tumours with a technologically advanced radiotherapy department and Australia's largest PET Centre, which acquired a PET/CT scanner in 2003. A feasibility proposal for the study was presented at the annual meeting of TROG, the Trans-Tasman Radiation Oncology Group which conducts most of the Australasian clinical trials in radiotherapy, in April 2004, and discussed with other interested centres at various national conferences of radiation, medical and surgical oncologists, all agreeing on the single centre policy. In April 2004 a team from the Austin Radiation Oncology Centre visited Dr Stevens at MD Anderson for training in mesothelioma IMRT, confirming that the early results were maintained and that side effects were tolerable [18].

The vast majority of patients with mesothelioma present with local symptoms confined to one hemithorax, and most recur after surgery in the same area, despite intraoperative or postoperative chemotherapy and conventional radiotherapy [19]. The establishment and maintenance of local control is therefore a major goal of treatment, and until more effective systemic agents become available, the local therapies of radical surgery followed by targeted large field postoperative radiotherapy are essential components for cure. Although extrapleural pneumonectomy followed by IMRT encompassing all sites of microscopic residual disease is highly successful, only a small proportion of mesothelioma patients are suitable to undergo this radical procedure. Those who are older with reduced respiratory reserves and comorbidities are eligible for the shorter operation of pleurectomy/decortication, and we are therefore attempting to develop a modified form of IMRT which spares more of the ipsilateral lung than the MD Anderson technique. This approach is being investigated at other centres, with little success to date [20]. Problems to be considered include treating the diagonal interlobar fissures, margins for respiratory movement and disease progression outside the planned target volume in the interval between surgery and the completion of radiotherapy. This interval frequently exceeds four months in order to incorporate time for surgical recuperation, wound healing, pain control,

radiotherapy planning, ability to remain immobilised during simulation and for 45 minutes per fraction over six weeks.

Potential solutions to these difficulties are currently being assessed. We hope that the inclusion of intraoperative phototherapy will improve sterilisation of microscopic residual mesothelioma cells at the margins of surgical resection, including the interlobar fissures. Hematoporphyrin derivative (HpD) is a first generation photosensitiser which has been used in 140 patients at the Austin since 1989 without any significant toxicity. The use of. neoadjuvant chemotherapy may retard short-term tumour progression following surgery in addition to improving operability by shrinking large masses of tumour [21, 22]. Most normal tissues can be spared excessive radiation by adopting IMRT, but the lung becomes the dose-limiting structure. The removal of all macroscopic disease at pleurectomy by performing when appropriate chest wall resection, lymphadenectomy and reconstruction of the diaphragm and pericardium (as is standard for EPP) will reduce the radiation dose required, but it remains very difficult to spare lung in the centre of a large tumour volume with current techniques. A recent report from Sugarbaker's group in Boston has warned of the high risk of acute pneumonitis following IMRT irradiation to the contralateral lung in patients who have undergone pneumonectomy and adjuvant chemotherapy, with six fatalities in their first thirteen cases [23]. To reduce the risk of pneumonitis one other option is to consider amifostine, a radioprotectant which in a recent meta-analysis of randomized trial data was found to raise the threshold for acute radiation pneumonitis and oesophagitis, while enhancing tumour response rates from radical radiotherapy [24]. This agent, in common with premetrexed, is not subsidised for this indication in Australia and is seldom used.

We have completed postoperative radiotherapy using high dose 3D-conformal radiotherapy on 13 patients between July 2003 and February 2006. Eleven have been referred following surgery by pleurectomy/decortication with intraoperative phototherapy using HpD at the Austin

Hospital, and a further two patients were resected elsewhere by EPP and radical pleurectomy that resulted in complete macroscopic disease resection. Radiation doses ranged from 45 to 60 Gy in 25 to 30 fractions, using a complex arrangement of 7-21 beams to meet the planning constraints set by Stevens et al [18]. Treatment plans were based on simulation CT scans fused with PET scans where available, using CMS planning software. This technology has enabled us to assess whether any relapses have occurred within the planned target volume (PTV) at followup.

Nausea and vomiting experienced by our early cases have been almost completely controlled with prophylactic 5HT3 receptor antagonist antiemetics, with most patients experiencing grade II radiation dermatitis, tiredness and weight loss. All have completed treatment on schedule and recovered their previous performance status in all but one case, who died 2 months after radiotherapy after pneumonia. No patient has had any grade 3 or 4 toxicities following radiotherapy, and in particular none have required steroids for pneumonitis. There has been one case of partial liver necrosis which completely resolved within three months. Median followup is six months post-radiotherapy.

Regular clinical, CT scan and PET scan assessments and serum mesothelin assays have been performed. Of 12 assessable patients, six patients have died, five with recurrent mesothelioma outside the irradiated field and one from a late surgical complication with no disease recurrence at nine months. Five are alive with progressive disease and one is alive with no recurrence at 13 months. Followup PET scans have shown significantly reduced FDG-avidity in all irradiated areas at assessment 3 months post-treatment, with progressive disease at sites beyond the planned targets in six cases (Figure 2). Patients have experienced lengthy delays between surgery and radiotherapy to allow time for surgical recuperation, wound healing, pain control, radiotherapy planning and ability to lie immobilised for 1 hour treatments and we have not repeated their imaging studies after simulation to incorporate new sites of disease in the PTVs.

Time taken to produce an acceptable treatment plan often exceeded one month due to difficulties in satisfying normal tissue tolerance constraints in the presence of unresected gross disease, and in the majority of cases we have compromised our target volume in order to reduce the risk of radiation toxicity, primarily to the lung. In one case who had received chemotherapy before resection in order to downstage disease, we recommended further combination chemotherapy in the planning interval following surgery to reduce the volume of active disease. Our compromised plans were unsuitable for an IMRT approach as the added complexities increased the daily fraction times from ten to forty minutes, and only one patient had the full hemithorax irradiated.

We succeeded in treating our first suitable patient with IMRT in May 2006. A dose of 50-60 Gy in 25 fractions was delivered through 6 fields to the lower hemithorax and upper abdomen after a PET/CT scan detected recurrence following PD and phototherapy one year previously. A concomitant boost was used (Figure 3), allowing of shortening the treatment time to five weeks instead of six, and all of the planning targets received doses which met the standard constraints (Figures 4,5).

Future proposals include considering neoadjuvant chemotherapy with four cycles of cisplatin and pemetrexed in fully staged patients before surgery, and adopting more aggressive approaches to tumour resection. We will refine our IMRT technique with fused PET/CT scans performed at the time of simulation incorporating full immobilisation in the treatment position.

Clinical trials of systemic therapy for mesothelioma in Australia

The majority of patients with mesothelioma present with advanced disease, with no realistic hope of cure from surgical or multimodality therapies. Systemic therapies aimed at palliating symptoms, improving health-related quality of life, and increasing survival are often the best

treatment options available. Until recently, malignant mesothelioma was a disease in which novel chemotherapy combinations could be readily trialed (and usually were) in a first-line setting. However, publication of the landmark clinical trial of cisplatin and pemetrexed by Vogelzang et al in 2003 has led to a worldwide change in the standard of care for this disease. This clinical trial was the first to show a survival benefit for any form of treatment in malignant pleural mesothelioma. The combination of the multitargeted anti-folate drug pemetrexed (Alimta®) in combination with cisplatin, as compared with cisplatin alone, gave a median survival of 12.1 months versus 9.3 months (p=0.02), and objective response rates of 41% versus 17% (p=0.0001) [25]. In addition to objective responses and a survival benefit, the authors reported small but statistically significant benefits for the combination arm in global QOL and symptom distress measures, and larger benefits for pain, dyspnea and cough after 18 weeks of treatment [26]. Recently, a smaller European study indicated a similar survival benefit with the use of the antifolate raltitrexed in combination with cisplatin compared with cisplatin alone, without detriment in health-related quality of life [27]

In the light of these results, the use of first-line combination chemotherapy with cisplatin and pemetrexed has become a standard approach in countries where this expensive combination is approved and funded. In Australia, pemetrexed is widely available for patients with malignant mesothelioma in New South Wales (mainly for compensated patients often through the Dust Related Diseases Board of NSW (DDB)), and Western Australia (for all patients). Furthermore, the availability of financial compensation for patients from other states with this disease means that many patients can self-fund treatment with pemetrexed and a platinum.

With the more widespread availability of an accepted first-line systemic therapy in this disease, clinical trials of chemotherapy or other novel agents have now moved into a second-line setting. This will create new problems in clinical trial methodology, in particular, difficulties in choosing the appropriate response rates for considering second line therapy activity ‘of interest’, when there are no benchmarks for a response rate considered to provide clinical benefit in this

setting. Combination chemotherapy that gives responses in the first line setting may not do so in the second line setting. Whilst the combination of oxaliplatin and raltitrexed showed objective responses of 20% and stable disease rates of 46% in a clinical trial enrolling predominantly first-line patients [28], in a subsequent trial of this combination as second-line treatment no objective responses were seen, and fewer than 30% of patients achieved stable disease as their best response. The median time to progression was 8 weeks [29]. In a phase II trial of the new generation platinum analogue ZD0473 in 43 patients, no objective responses were seen and the median time to tumour progression was 11 weeks [30]. What response rates will indicate an active agent with potential for translation to the first-line setting? What response rates should we expect (if any) from novel cytostatic agents, and how should our clinical trial endpoints be selected to reflect this changing paradigm?

Currently, there are no clinical trials of first line chemotherapy in mesothelioma in Australia, and 3 clinical trials of second-line or maintenance therapy. Work on assessment of disease response is also ongoing, with prospective data on PET scanning in mesothelioma being undertaken.

A phase II study of Sutent (SU11248) in the second line treatment of malignant pleural mesothelioma

Among a range of potential therapeutic targets in mesothelioma are the vascular endothelial growth factor family of transmembrane growth factor receptors (VEGFR1, 2 & 3) and the receptors for platelet derived growth factor (PDGFR α & β). VEGF is an autocrine growth factor in human malignant mesothelioma and may be a key regulator of mesothelioma growth [31]. An inverse relationship between serum levels of VEGF and survival in mesothelioma has been reported [32]. In human mesothelioma co-expression of VEGF and its receptor has been demonstrated by immunohistochemistry and in situ hybridisation, as has expression of VEGF-C and its corresponding receptor VEGFR-3 [31, 33]. In addition antibodies to VEGFR-2 and

VEGFR-3 have been shown to act synergistically to inhibit mesothelioma cell growth in vitro [31]. PDGF and both PDGFR α and β are expressed in mesothelioma cell lines [34], and immunohistochemical staining detected PDGFR β in 100% of a small series of cases [35]. These and other data suggest that both the VEGF and PDGF family are activated in malignant mesothelioma and may provide potential targets for anti-tumour therapy.

Sunitinib (Sutent, SU11248) is an orally administered small molecule multi-targeted tyrosine kinase inhibitor. It is a potent inhibitor of the tyrosine kinase activity of the Class 3 and Class 5 split-kinase domain receptor tyrosine kinases, including the PDGF and VEGF receptors, KIT (a receptor for stem cell factor (SCF)), and FLT-3. Receptor tyrosine kinases are transmembrane proteins containing extracellular ligand binding domains and intracellular catalytic domains. They are activated following binding of their cognate ligands. Most of the processes involved in tumour growth, progression and metastasis are mediated by signaling molecules acting downstream from receptor tyrosine kinases [36]. Several members of this family of receptor tyrosine kinases may be involved in autocrine proliferation and survival of solid tumours, including the PDGF receptors (PDGFRα and β), VEGF receptors types 1 and 2, KIT, FLT-3, and RET. Expression of split kinase domain receptor tyrosine kinases on solid tumour cells may promote cell growth and survival by autocrine loops or mutations. PDGFR and VEGFR are also important for tumour neoangiogenesis [37]. VEGF is produced by tumour and associated stromal cells and can promote proliferation, migration, invasion and survival of endothelial cells [38]. Combined inhibition of PDGFRβ and VEGFR-2 in mice leads to rapid vessel killing in tumours, with potent antitumour effects [39]. In subcutaneous xenograft tumor models, oral sunitinib administration results in potent inhibition of tumor growth, causing regression or stasis of large established tumors of multiple origins, and inhibiting growth of metastases. Sunitinib has also been tested in phase I studies, and has an acceptable toxicity profile with grade 3 fatigue (8%), neutropenia (8%) and gastrointestinal toxicity (2%) the most prominent side effects [40]. In a recent phase III study in patients with renal carcinoma, sunitinib demonstrated

a a highly clinically and statistically significant advantage in progression-free survival and response rate over interferon-alpha [41], and this drug is quickly moving into the therapeutic armamentarium in this disease. Sunitinib also shows activity in patients with previously treated metastatic breast cancer [42], and is US FDA approved for Imatinib-resistant gastrointestinal stromal tumours (GIST) and renal cell carcinoma [43].

Its oral availability, acceptable toxicity profile and multi-targeted spectrum of receptor tyrosine kinase inhibition suggested its potential for significant anti-tumour activity in mesothelioma. This is a non-randomised single centre phase II study of single-agent sunitinib as second line therapy in mesothelioma, underway at Sir Charles Gairdner Hospital in Western Australia. Eligibility requirements are for a histologically or cytologically confirmed diagnosis of pleural malignant mesothelioma, previous therapy with at least one cycle of a platinum analogue and an antimetabolite with documented progression on or after completion of first-line therapy, an ECOG performance status of 0-1, measurable disease, a life expectancy >12 weeks, adequate organ function, and written informed consent. Exclusion criteria are standard, with the exception that patients with a prior talc pleuradesis are excluded. Patients with prior talc pleuradesis are ineligible as this renders changes on PET scan, a response criterion, more difficult to interpret reliably, due to residual pleural inflammation from the procedure.

The primary endpoint of the trial is objective response rate as assessed by the Modified RECIST Criteria [44] and by response on PET scan. Secondary endpoints include time to tumour progression, time to treatment failure, overall survival, change in lung function tests, toxicity, and change in serum mesothelin levels. In addition to objective tumour response, visual and quantitative assessment of the change in tumour metabolism after one cycle of treatment will be assessed by serial [F-18] FDG PET scans. Quantitative indices of total glycolytic volume (TGV) and tumour volume (TV) have been related to tumour response to chemotherapy in a first line treatment setting in patients with MPM [45, 46].Changes in the standard uptake value

(SUV) as measured with PET have previously been used as an index of antitumour activity with sunitinib [47].

All patients will receive sunitinib 50 mg daily orally for four weeks, followed by two weeks off treatment each 6-week cycle. Dose modifications are specified for toxicity. Most endpoints are assessed 6 weekly. The sample size has been calculated using Simon's optimal two-stage design, with an initial 23 patients and a maximum of 51 patients recruited assuming a response rate of 20% to be of interest and a response rate of 5% to be of no interest. Recruitment over approximately two years is anticipated. The study commenced recruiting in June 2006.

A conventional phase II study design using single-agent sunitinib as second line therapy may reveal activity in this patient population, however prolongation of time to progression may also indicate potential for sunitinib following response to first-line chemotherapy or following multimodality therapy including surgical resection for early stage mesothelioma. Any activity would justify the early development of protocols in a first line setting.

The MATES Study – Maintenance Thalidomide in mESothelioma.

Thalidomide, a sedative first used in pregnancy in the late 1950s with subsequent devastatingly detrimental effects on embryogenesis, was re-discovered in the 1990s as an anticancer agent after being shown to inhibit bFGF and VEGF mediated angiogenesis together with it's cytokine modulatory properties, in particular involving interleukin-6 and tumour necrosis factor alpha [48-50]. Two Phase II clinical trials involving thalidomide have been reported. In the first published Phase II study conducted in the Netherlands (N = 42, 20 received prior chemotherapy), thalidomide up to 400 mg daily did not produce any tumour responses however 11 of the 40 patients (27.5%) could be treated with the drug for 6 months or longer showing stabilization of the disease [51]. Side effects were manageable

and consisted of sleepiness, constipation and in two patients neurological toxicity grade 2 and 3 was observed.

In Australia, a parallel design Phase II study was conducted investigating the activity of thalidomide in combination with cisplatin/gemcitabine (C/G) chemotherapy (Arm A) or alone (Arm B) in patients with advanced malignant pleural mesothelioma [52]. Thalidomide was administered alone (arm B) (100 – 500 mg p.o./d), or in combination with weekly i.v. C (25 mg/m^2)/G (800 mg/m^2) chemotherapy (D1, 8,15 Q4 weekly) (arm A). The primary objective was response rate (PR = partial response, PD = progressive disease, SD = stable disease). Eligibility criteria included no prior chemotherapy (arm A) or prior chemotherapy or medically unsuitable for chemotherapy (arm B). 63 patients were enrolled: 34 in arm A, 29 in arm B (9 (31%) having prior chemotherapy); 7 female and 27 male (A); 4 female and 25 male (B); median age 59 (A) and 67 (B). In the combination arm there were only 3 PR (14%) whilst in the thalidomide alone arm 8 patients (27%) had stable disease for > 6 months. Median tolerated thalidomide dose was 200 mg (both arms). Common toxicities from thalidomide included mild constipation, dry mouth, fatigue, dizziness and parasthesiae (B). Exploratory analysis of serum VEGF indicated a possible prognostic role with worse survival associated with high baseline serum VEGF. These results confirmed the findings from the Netherlands Cancer Institute Phase II study and raised the hypothesis that thalidomide may delay disease progression.

Based on these Phase II findings, an Open label Randomized Phase III study of Thalidomide as maintenance therapy in non-progressing patients after first line Alimta based chemotherapy was commenced in the Netherlands in 2004 (The NVALT5 Study, Dr P Baas). A similarly designed study was proposed in Australia by the ALTG and the two groups agreed to co-operate in the one study. The Australian study includes two sub-studies: one addressing QoL, using several established tools, and the other exploring the predictive/prognostic value of a series of serum biomarkers, including

VEGF, mesothelin and osteopontin: The Mates study -Maintenance Thalidomide's Effectiveness, Safety, and Quality of Life after chemotherapy for mesothelioma.

Participation in international pharmaceutical industry initiated clinical trials

Australian sites participate in international clinical trials initiated by the pharmaceutical industry. Participation in other international industry-initiated clinical trials of novel agents is currently under discussion.

SAHA second line in mesothelioma

Histone deacetylase (HDAC) is an enzyme involved in removing acetyl groups from histones and other proteins. An imbalance in histone acetylation may lead to transcriptional dysregulation of genes involved in the control of cell cycle progression, differentiation, and apoptosis [53]. HDAC inhibitors are a novel class of agents shown to induce tumor cell growth arrest, differentiation, or apoptosis in vitro and inhibit tumor growth in animals [53]. A number of HDAC inhibitors have entered clinical trials [53]. Among these agents, Suberoylanilide Hydroxamic Acid – SAHA (L-001079038) is a potent inhibitor of HDAC that can be administered orally with good bioavailability. In a Phase I study of oral L-001079038 in patients with advanced solid tumors and hematologic malignancies, 13 patients with mesothelioma who had failed front-line therapy were enrolled. Two patients responded with decreases in tumor mass and pleural effusion and improvement of tumor-related pain or shortness of breath. Based on this finding and the unmet need for exploration of novel therapies beyond pemetrexed and cisplatin for mesothelioma patients, an international Phase III study has been initiated by Merck: A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial of Oral Suberoylanilide Hydroxamic Acid (L-001079038) in Patients With

Advanced Malignant Pleural Mesothelioma Previously Treated With Systemic Chemotherapy. Several centres in Australia are participating in this study.

Clinical trial methodology studies in Australia

Measurement of response for clinical trials of mesothelioma has been an active area of research in Australia. Malignant mesothelioma grows as a 'rind' around the thoracic cavity, rather than in a roughly spherical fashion like many other neoplasms. This made measurement by the WHO criteria and, more recently, the RECIST criteria, difficult to perform and to reproduce between centres and investigators. The Modified RECIST Criteria [44] are now in widespread use in mesothelioma clinical trials, and go some way towards addressing these problems. Partial response as assessed by the Modified RECIST Criteria correlates with relief of symptoms, improvement in lung function tests and health-related quality of life, and patient survival. However, application of these modified criteria is still time consuming, and inter-observer reliability has not been validated. Furthermore, it is often not clear whether patients are responding to chemotherapy until several cycles of treatment have been given. In a previous study, we found that of those patients achieving a partial response, only 47% did so after one treatment cycle, and the median time taken to achieve a radiological partial response was four cycles [5]. Clearly, this means that many patients are exposed to more cycles of chemotherapy and thus more toxicity, when they may not be deriving benefit from treatment. If patients could be identified early as unlikely to benefit from treatment, they could be spared further side-effects, and potentially enrolled in clinical trials of second-line therapy whilst their performance status was preserved.

Use of FDG PET in the Assessment of Tumour Extent and Tumour Response in Pleural Mesothelioma

The considerations discussed above led to work investigating the use of FDG PET to stage mesothelioma at presentation, and to assess response to chemotherapy. ^{18}F FDG PET scans measure the metabolic activity, and therefore the viability, of tumour cells. Serial changes in ^{18}F FDG uptake can predict response in other tumour types after just one cycle of chemotherapy [54-56]. Mesothelioma has been demonstrated to be FDG PET avid [57-59]. This ongoing single-centre prospective cohort study at Sir Charles Gairdner Hospital in Western Australia has accrued over 50 eligible patients to date for assessment of staging of disease and, in those patients who go on to have chemotherapy as part of their routine clinical care, for assessment of response to treatment. Eligible consenting patients have confirmed malignant pleural mesothelioma, and those on the response study are planned to have chemotherapy as part of their routine clinical care. The important exclusion criterion is past pleuradesis, which renders PET scans difficult to interpret even many months after the procedure [60]. The staging study aims to define the PET appearance in patients with masses visible on CAT scan and those with effusion only, to examine the incidence and extent of cryptic metastatic disease demonstrated by PET scan compared to routine CAT scanning, to assess the relationship of the PET appearance to the histological subtype of mesothelioma, and to evaluate whether the PET appearance provides prognostic information. The response study aims to assess the sensitivity and specificity of FDG PET scan changes after one cycle of chemotherapy to predict ultimate response to chemotherapy, time to progression and overall survival, and to assess the relationship between HRQL changes and tumour volume and PET scan changes.

There are no formal guidelines for measurement of response to chemotherapy using ^{18}F FDG PET in solid tumours, and other authors have used visual analysis, maximum standardised uptake values (SUVmax), or mean standardised uptake values (SUVmean) to assess response. However, as well as posing challenges for measurement of radiological response, mesothelioma also brings particular challenges for measurement of response by PET scanning. The disease is often diffuse and heterogenous, and it is difficult to select a representative site as SUVmax.

Furthermore, SUVmax represents only one pixel of the often large and complex tumour mass. Novel semi-automated software has been developed for this study, which uses a region-growing algorithm to define the 3-dimensional boundaries of the tumour, giving a measure of the total glycolytic volume (TGV) of the mass [45]. This software shows excellent inter-observer reliability and is simple to use (Francis R et al, personal communication May 2006). Preliminary results have been reported for the response study, showing that ^{18}F FDG PET response after one cycle of chemotherapy is a better predictor of survival outcomes than CT scan response at this time [45, 46]. This technique appears promising as a surrogate measure of clinical benefit, and as an outcome measure in future clinical trials in mesothelioma.

Conclusion:

Despite the small population of Australia, the high incidence of malignant mesothelioma and the concentration of healthcare resources and expertise in major population centres has led to considerable activity in mesothelioma research. Working within limitations in research funding, investigators continue to develop clinical trials and clinical trials methodology. Furthermore, the small number of investigators and concentration of patients with mesothelioma at relatively few sites make Australia a favourable country for activity by the pharmaceutical industry. Results from ongoing clinical trials described should be available within the next few years, and will hopefully make a substantial contribution to the body of knowledge in this devastating disease.

Legends to the Figures:

Figure 1: Children playing in crocidolite asbestos tailings, Wittenoom, Western Australia. Both subsequently died of malignant mesothelioma in adulthood.

Figure 2: Patient positioned for IMRT with immobilisation support, showing skin reaction on last day of treatment.

Figure 3: Digital reconstruction radiograph showing organs at risk with planning target volume (PTV, delineated by white wired volume, and boost planning target volume (bPTV) treated to 50 Gy and 60 Gy respectively in 25 fractions

Figure 4: Digital reconstruction radiograph of anterior IMRT field, with electronic portal image of treatment exposure showing intensity modulation of beamlets delivering varying doses over the treatment volume, allowing protection of organs at risk. The full length of this field is too long to fit on the standard viewer.

Figure 5: Transverse cuts of treatment plan at two levels with isodose contours for 20, 50 and 60 Gy, encompassing planning target volume. The dose to radiosensitive normal tissues including contralateral lung, heart, liver and spinal cord are within tolerance limits.

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