

CLINICAL VIGNETTE

New Results and Concepts in Systemic Treatment of Mesothelioma

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Malignant Mesothelioma is rare cancer that arises from the layer of mesothelial cells. Mesothelial cells usually line the surfaces of the lungs, heart, peritoneal cavity and tunica vaginalis. Most of the mesotheliomas (80%) are of pleural origin.

Mesothelioma is a rare cancer with incidence of 2000- 3000 cases reported each year in the United States. Mesothelioma is strongly associated with exposure to asbestos. The tumor forms after asbestos particles are inhaled, and subsequently lodge in the lining of the airways and the lung. The latency period between the exposure and development of disease is at least 15 years, with risk persisting for decades. Most patients present in the 6-8 decade of life. Asbestos was used extensively in the past in this country, and is still used in other countries as an insulation material.

Histologically, mesothelioma can be subdivided into three types. Epithelioid, sarcomatoid and biphasic. Traditionally the biphasic and sarcomatoid types have worse prognosis and survival than the epithelioid type. If the disease is localized to one hemithorax, the primary approach is pleurectomy and decortication followed by radiation. However, for more widespread or recurrent disease chemotherapy has been the mainstay of treatment.

Almost all chemotherapeutic agents have been tried in mesothelioma. Prior to 2003 there was no standardized therapy. A meta analysis of 119 trials demonstrated that combination therapy, especially cisplatin based regimens, provided better response rate than single agent therapy.

In 2003, two International Trials demonstrated that combination therapy with either pemetrexed or raltitrexed increases survival compared to single agent cisplatin. Both trials showed a significant increase in response rate, and no deleterious impact on quality of life.

Pemetrexed is an antifolate that inhibits purine and pyrimidine synthesis. It inhibits key

enzymes such as Thymidilate Synthase (TS), Dihydrofolate Reductase (DHFR) and Glycinamide Ribonucleotide Transferase (GARFT), which are required in DNA synthesis. Cisplatin acts by intercalating itself among the DNA bases, and thus inhibits DNA synthesis. Vogelzang published the major US trial in 2003 comparing combined therapy to cisplatin alone. This phase III trial randomized 456 patients with unresectable mesothelioma who were chemotherapy naïve. 226 patients received cisplatin at 75 mg/m² with pemetrexed 500mg/m² on a 21-day schedule compared with 222 patients with cisplatin alone. This was the first trial to demonstrate superior Overall Survival (OS) (12.1 mos vs 9.3mos), Time To Progression (TTP) (5.7 mos vs 4.9 mos) and Response Rate (RR) (41.3% vs 16.7%) in the combination arm. The study established the combination of cisplatin 75mg/m² and pemetrexed (500mg/m²) every 3 weeks as the new standard of care.¹ Similar results were achieved when antifolate raltitrexed was combined with cisplatin in a phase III EORTC trial^{2,3}. The current recommendation is to administer at least 4 courses of Cisplatin 75mg/m²+Pemetrexed 500 mg/m².⁴ If delayed response is seen and therapy is tolerated, treatment can be extended to 6 courses. When pemetrexed is used, folic acid and Vitamin B12 supplementation are required to decrease hematologic toxicity.

The question whether carboplatin can be substituted for cisplatin was evaluated in an International Extended Access Program (EAP). This multicenter, nonrandomized, open label trial in chemotherapy naïve patients compared Pemetrexed + Cisplatin (n= 843) versus Pemetrexed + Carboplatin (n=861)⁵. The overall Response Rate was 26.3% in the cisplatin arm, and 21.7% in the carboplatin arm respectively. Time to Progression (TTP) was 7 months in the cisplatin arm and 6.9 months in the carboplatin arm. One-year survival rates were comparable, 63.1% for cisplatin and 64% for carboplatin.

Therefore at this time, Cisplatin and pemetrexed is the regimen of choice, and the only FDA approved regimen. However substituting Carboplatin for Cisplatin may be acceptable.

Another issue is whether patients can be re-treated with pemetrexed at progression. In a Phase III trial conducted by Jassem, patients with progressive disease were randomized to best supportive care or second line pemetrexed (single agent). Significantly better response rate (18.7 vs 1.7%) and longer time to progression (3.7 mos vs 1.7 mos) were seen in patients re-treated with pemetrexed, but there was no difference in overall survival⁶.

The role of maintenance therapy remains to be determined. The CALGB 30901 trial is an ongoing multicenter randomized phase II trial of maintenance pemetrexed vs observation⁷. The goal of the trial is to determine whether maintenance therapy with pemetrexed improves PFS and OS. Patients are randomized to pemetrexed 500mg/m² q 21 days vs observation alone, after completing four cycles of pemetrexed/cisplatin regimen. The trial is due to close December of 2015.

The role of biomarkers has always been a challenging topic in the field of oncology. As we saw from the pivotal pemetrexed trial only 40 % of the patients responded to cisplatin/pemetrexed regimen. Several biomarkers were investigated in order to establish which patients will respond to the chemotherapy. The role of thymidilate synthase, which is the main enzyme in the synthesis of pyrimidines inhibited by pemetrexed, was examined in relation to response to pemetrexed. The role of Excision Repair Cross-Complementation Group 1 (ERCC1), a DNA damage repair gene in the nucleotide excision repair pathway, which removes cisplatin induced DNA adducts, was also evaluated to assess response to cisplatin.

In an Italian Retrospective study⁸, Righi collected data on 60 patients with confirmed MPM previously treated with pemetrexed and platinum (45 of 60) or single agent platinum (15 of 60). The investigators looked at Thymidilate Synthase and Excision Repair Cross-Complementation Group 1 (ERCC1). Gene expression levels were evaluated by Polymerase chain reaction (PCR). Protein levels were evaluated by Immunohistochemistry (IHC). In

patients treated with pemetrexed, low Thymidilate Synthase protein levels (gold line) were predictive of improved time to progression (TTP) 17.9 vs 7.9 mos, as well as longer OS 30 vs 16.7 mos. Baseline TS values had no prognostic value in patients not treated with pemetrexed⁸. (Figure 1)

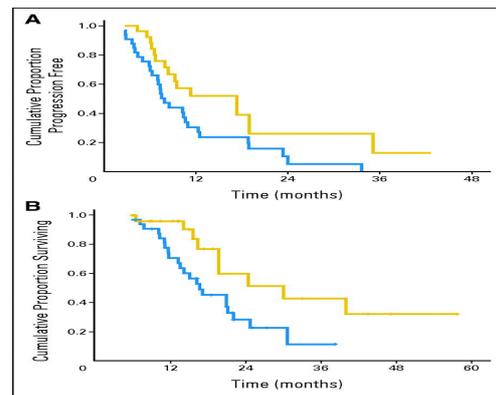


Figure 1. Gold line: Low TS Blue line: High TS

Excision repair cross- complementation group, ERCC1, was evaluated in patients treated with platinum based therapy. ERCC1 was a prognostic factor; patients with high ERCC1 levels had longer median survival than patients with lower ERCC1 protein expression, (30 months vs 19.7 months) regardless of the chemotherapy regimen employed. No correlation between ERCC1 levels and response to cisplatin or carboplatin was found⁸. (Figure 2)

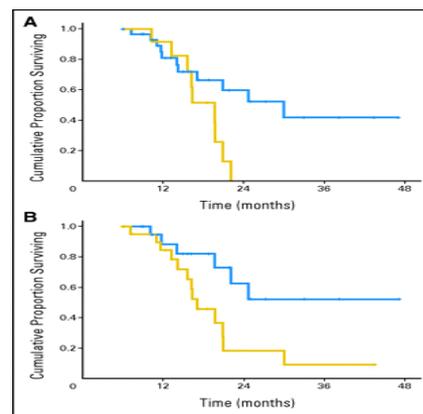


Figure 2. Blue line: High ERCC1 Gold line: Low ERCC1 .

Other chemotherapy agents are still used in mesothelioma treatment.

Gemcitabine, is a nucleoside analogue of deoxycytidine, in which two fluorine atoms have been inserted into the deoxyribose ring. It competes for incorporation into DNA thereby inhibiting DNA synthesis. Prior to introduction of Pemetrexed, gemcitabine and cisplatin had been used as first line treatment in mesothelioma with responses between 12-48%.

Patients with mesothelioma have very high levels of Vascular Endothelial Growth Factor (VEGF). In a phase II trial, Anti-VEGF Antibody bevacizumab was added to cisplatin/ gemcitabine combination in first line patients with unresectable mesothelioma⁹. Patients were randomised to receive Gemcitabine 1250 mg/m² day 1, 8, Cisplatin 75 mg/m² on day 1, bevacizumab 15 mg/kg on day 1, every 21 days for 6 cycles, or gemcitabine 1250 mg/m² day 1, 8, Cisplatin 75 mg/m² on day 1 and placebo on day 1. If they had stable disease at completion of 6 cycles, they received bevacizumab 15 mg/kg vs placebo every 21 days until progression. Unfortunately, addition of bevacizumab did not improve PFS or OS. PFS was 6.9 months in bevacizumab arm, and 6 months in placebo arm (P=0.88). OS was 15.6 months in bevacizumab arm and 14.7 in placebo arm. However, difference in OS was seen if patients were stratified by baseline VEGF levels. Patients with higher baseline VEGF levels had worse PFS and OS. VEGF levels were not different between responders and non-responders. At the beginning of the trial pemetrexed was not available, and now there is information about negative interaction between gemcitabine and bevacizumab.

An ongoing MAPS Trial, a multicenter randomized phase III trial of pemetrexed-cisplatin with or without bevacizumab, is addressing the question of bevacizumab therapy in patients with malignant pleural mesothelioma¹⁰. As of April 30, 2012, 280 patients from 85 French Centers had been enrolled, with 8.9% difference in OS in patients receiving bevacizumab in addition to pemetrexed and cisplatin. Biomarker Analysis of Tissue Specimens is also ongoing.

There is no standardized second line therapy, since there is no FDA approved agent or drug in clinical trials that has demonstrated a survival advantage. The following agents have completed phase II trials. Anti-angiogenic agents/Tyrosine Kinase Inhibitors: Thalidomide, Sunitinib,

Cedarinib, Sorafenib. Tyrosine Kinase Inhibitor Dasatinib. Histone Deacetylase inhibitor Vorinostat. An ongoing trial is evaluating CTLA-4 antibody, tremilumab.

A summary of the studies follows.

NVALT was an open label randomized phase III study of maintenance thalidomide vs. placebo. Patients who completed 4 cycles of pemetrexed based therapy were randomized to receive either thalidomide 200 mg/day, or placebo. At 33 months, no difference was seen in survival or time to progression. More adverse events were reported in thalidomide group (neurosensory and cardiac)¹¹.

Sorafenib is a potent inhibitor of the ras/raf/MEK pathway, which also targets VEGFR and cKIT. A phase II study was conducted in malignant mesothelioma patients who had received 0 to 1 prior chemotherapy regimens. Sorafenib 400 mg was administered orally twice daily continuously, vs placebo. Response rate was 6%, with no difference in OS (9.7 months/ OS 9.0 months) or PFS 3.6 months/ 5.1 months^{12,13}.

Sunitinib is an antiangiogenic inhibitor of multiple tyrosine kinases in the VEGFR, PDGFR, c-kit, FLT-3 pathways. Second line Phase II study evaluated administration of intermittent sunitinib 50 mg daily for 28 days of 42 days. 53 patients were evaluated from July 2006-Dec 2009. 12% response rate was seen, with 65% disease stabilization. Median Time to Progression was 3.5 months. OS was 6.7 months¹⁴.

Cedarinib is an oral tyrosine kinase inhibitor of VEGF receptor family (VEGF receptors 1,2,3) that has been studied in two phase II clinical trials. SWOG Cedarinib S0509¹⁵ included 54 patients and the University of Chicago Phase II Consortium, 51 patients¹⁶. All patients previously treated with platinum-containing chemotherapy received Cedarinib 45 mg orally daily. The primary end point was objective response.

Both trials demonstrated 9%-10% RR, 34% disease stabilization and modest PFS 2.6/1.8 months respectively. However grade 3/4 adverse events such as fatigue, hypertension, pulmonary embolism, angioedema, and reversible posterior leukoencephalopathy were observed.

Dasatinib is an aminothiazole analogue, an oral tyrosine kinase inhibitor which belongs to a family of SRC family kinases (SFKs), which also inhibits vascular endothelial growth factor (VEGF), and platelet-derived growth factor β (PDGF β) receptor. Phase II study of dasatinib, in patients with previously treated malignant mesothelioma was conducted by the Cancer and Leukemia Group B 30601¹⁷. Patients previously treated with chemotherapy were eligible. Biomarker Analysis included levels of vascular endothelial growth factor, platelet-derived growth factor b, colony stimulating factor 1 (CSF-1) and mesothelin-related protein, measured at baseline and during therapy. Dasatinib was administered at 50 mg orally daily and 46 patients were evaluated. Disease control rate was 32.6%, progression-free survival was 9.1 weeks, overall survival was 26.1 weeks. Grade 3 and 4 toxicities included fatigue (11%) and pleural effusion (9%). Survival was markedly longer in patients with lower pretreatment Colony stimulating factor 1 (CSF-1) levels and in patients whose CSF-1 levels decreased from baseline during therapy. (Figure 3)

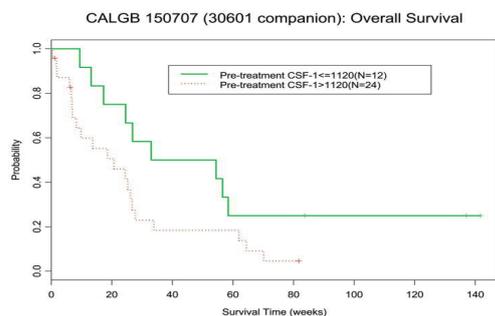


Figure 3

The potential role of Histone deacetylase inhibitor vorinostat. To carry out gene expression, a cell must control the coiling and uncoiling of DNA around histones – proteins in the cell around which the DNA coils. This is accomplished with the assistance of histone acetylases (HAT) which acetylate the lysine residues in core histones leading to a less compact and more transcriptionally active chromatin. Histone deacetylases (HDAC), remove the acetyl groups from the lysine residues leading to the formation of a condensed and transcriptionally silenced chromatin. Pre-clinical data suggests that HDACs play a role in the malignant transformation of mesothelioma. HDAC inhibitor Vorinostat demonstrated some activity in a Phase I trial, which led to a large

Phase III trial of Vorinostat vs placebo¹⁸. Vantage 014 was a multicenter phase III trial, that enrolled 660 patients with malignant mesothelioma, that were treated with no more than 2 prior therapies. They were randomized to receive Vorinostat 300 mg po bid for 3 days out of for 7 days, q 21 days until disease progression vs placebo. Primary outcome was progression free survival, secondary outcome was overall survival. No difference was seen on PFS (6.3 vs 6.1 weeks) or OS (31 vs 27 weeks).

Immunotherapy with tremilumab- CTLA 4 antibody. There has been a long standing interest in stimulating the immune system to treat cancer. Immune response is the body's natural mechanism of defense against cancer cells. Clinical testing of immune stimulating cytokines led to low frequency of durable responses. Interferons and interleukens are immune stimulating cytokines that have activity in several cancers such as melanoma and renal cell carcinoma.

Dendritic cells are antigen presenting cells. (Figure 4) They present processed tumor antigens to the T cell in the immune system. T cells are believed to be the main effectors of the immune system's antitumor response

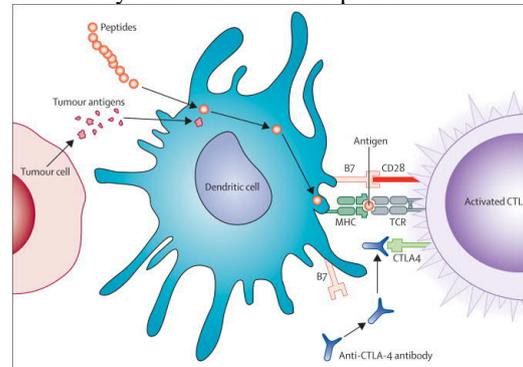


Figure 4

T cells recognize antigen presented by the dendritic cells when it is coupled with the Major Histocompatibility Complex (MHC) through their T-cell receptor. T cells generate an immune response by binding to a stimulatory receptor (B7) on the dendritic cell via the CD 28 receptor on the T cell. This activates the immune system, which results in increased production of activated T cells. Helper T cells secrete IL-2. Cytotoxic T cells (CTLs) directly target and lyse tumor cells expressing the antigen presented to them. To avoid overactivation of the immune system, there is an increased expression

of the Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), a transmembrane protein. CTLA-4 is expressed about 48 hours after T- cell activation. It competitively binds to B7, outcompeting stimulatory CD28 receptors. CTLA-4 binding provides dominant negative signaling and inhibits the immune response. Antibody to CTLA-4 prevents interaction with B7 and removes downregulation of the immune system. Blockade of this checkpoint provided the first evidence of improvement in OS in patients with metastatic melanoma¹⁹. CTLA-4 blockade with Monoclonal Antibodies (MoAbs) blocks the inhibitory signal, thereby sustaining activation and proliferation of T cells. Two agents are available, both human MoAbs. Ipilimumab was approved by FDA in 2011 for treatment of metastatic melanoma. Tremelimumab is currently in clinical trial as second line therapy in patients with malignant pleural mesothelioma.

A phase II, randomized, double-blind study comparing tremelimumab to placebo in second- or third- line treatment of subjects with unresectable Malignant Pleural Mesothelioma is currently open at UCLA. The study is planning to enroll 180 subjects who will be randomized 2:1 to receive tremelimumab or placebo. The primary objective is overall survival, and the secondary objectives include progression free survival, durable complete response, and a number of validated quality of life measures. Other outcomes include disease-related symptoms, pain symptoms, time to deterioration of disease-related symptoms, biomarker Analysis and their association with tremelimumab treatment and clinical outcome. Tumor assessments will be done with scans every three months and patient reported outcome assessments will be collected.

In a recent publication Hassan et. al describe the use of a antibody conjugates against mesothelin in the treatment of mesothelioma. Mesothelin is an antigen that is expressed by the mesothelioma cells. An antimesothelin antibody fragment combined with a portion of Pseudomonas exotoxin A(S1P) has been developed to recognize mesothelin on the cancer cell and then destroy the mesothelioma cell. The limitation in the past has been generation of antibodies to the anti mesothelin protein after the first cycle of therapy, precluding further treatment with the compound. Hassan et al recently reported using a conditioning regimen of cyclophosphamide and

pentostatin to eradicate T and B cells responsible for the antibody generation.

Out of the 10 heavily pre-treated patients, 3 had major tumor regressions. 2 of the patients had responses lasting for 15 months, and 2 additional patients responded to cytotoxic chemotherapy after discontinuing the immunotoxin^{20,21}.

Important changes in the management of mesothelioma have occurred in the past decade. Cisplatin/pemetrexed combination has been approved by the FDA, but the OS after the regimen is 12.1 months. Unfortunately there is no effective second line therapy that is FDA approved, and overall survival still remains dismal. Role of VEGF in first line treatment and maintenance is currently being investigated. Molecular-biologic studies are examining biomarkers and pathways. The role of immunotherapy is promising, with the anti CTLA-4 antibodies currently being studied. The role of immunoconjugates coupled with immune modulation appears to be promising and needs further study.

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