Invited Lecture 1

Advances in the Treatment of Mesothelioma

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Given our interest with malignant pleural mesothelioma (MPM) we seek to reduce the morbidity and mortality of the surgical procedures and extend survival through a combination of therapeutic approaches. Treatment strategies pursued involved different surgical approaches--extrapleural pneumonectomy (EPP) or pleurectomy/decortication (P/D)--and different combinations, regimens, and doses of adjuvant chemoradiotherapy. There has been a dramatic decline in the morbidity and mortality associated with these surgical techniques, new modalities for containing loco-regional recurrence have been introduced, and a long-term survival can be seen in selected patients (51 months).

The primary goal of either EPP or P/D is to achieve a macroscopically complete resection (MCR). Superior cytoreduction can be achieved with EPP; however, other co-morbidities, diminished cardiopulmonary status, or both, may preclude EPP for some patients. In such instances, if the patient has minimal disease, disease-free fissures, regionally located disease, and soft tumor, P/D may result in MCR, particularly if adjunctive intraoperative therapy aimed at eliminating microscopic pockets of disease is applied. Achieving MCR is not easy, however, as the disease can spread into the fissures with infiltration of pulmonary parenchyma, particularly with sarcomatoid or mixed cell types. In addition, the potential dose of adjuvant radiation therapy is diminished in patients with retained pulmonary parenchyma. In our view, each of these elements tip the argument in favor of EPP, provided that the patient is able to tolerate the surgery.

In 2004, we published a mortality rate of 4% for 496 patients who underwent EPP between 1980 and 2000. Findings from the subset of 328 MPM patients prospectively examined for detailed morbidity (60%) and mortality (3.4%) revealed the most common complications to be cardiac. Atrial fibrillation was most common with 145/328 patients (44%). Other complications included prolonged intubation (7.9%), vocal cord paralysis (6.7%), and deep venous thrombosis (6.4%). Less common complications consisted of tamponade, acute respiratory distress syndrome (ARDS), empyema, and renal failure.

One Phase I trials with EPP plus HIOC and sodium thiosulfate for renal projection established the MTD of 225 mg/m2 CDDP (cis-diamminedichloroplatinum) and the overall safety of IOHC. A second Phase I trial (99-124) was conducted in P/D plus IOHC and sodium thiosulfate and yielded similar results. Subsequently two Phase II studies were conducted to establish the efficacy/feasibility of IOHC with sodium thiosulfate in EPP (03-302) and P/D (04-063). Published results show a significant IOHC dose effect on survival. Low-dose (50-150mg/m2) IOHC CDDP demonstrated lower median survival (6 months) in comparison with high-dose (175-250mg/m2) CDDP (18 months) (p<0.0019).

Although attaining optimal MCR through surgical resection remains the cornerstone of treatment, adjuvant therapy is needed to reduce locoregional recurrence after surgery. Likewise, the efficacy of adjuvant therapy is based on the adequacy of the surgical resection. Significant progress made in chemotherapy (EMPHASIS, ALIMTA, IOHC), radiotherapy and various laser technologies has opened promising new avenues for destroying occult tumor cells at microscopic levels. Genetic studies published by our basic science group on aberrant patterns of gene expression in MPM may lead to less invasive diagnostic studies with greater sensitivity and specificity that could direct treatment based on genetic analysis. Our treatment strategies are constantly changing to take advantage of these parallel advances and we have been rewarded with a long-term survivors of MPM and are hopeful that future efforts to attack this disease on all fronts will deliver the ultimate goal of achieving a cure.