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Induction chemotherapy, extrapleural pneumonectomy, and radiotherapy in the treatment of malignant pleural mesothelioma: The Memorial Sloan-Kettering experience

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Summary Approximately 25% of patients with malignant pleural mesothelioma (MPM) prove unresectable at surgery and the median survival of stage III MPM is <12 months even after complete resection by extrapleural pneumonectomy. From 1939—2004, a series of sequential clinical trials has been performed at our institution. The surgical procedure has been modified and improved upon, and adjuvant hemithoracic radiation (RT) standardized. The evolution of our current standard of care for MPM is discussed. Improving chemotherapy for MPM led us to test induction chemotherapy followed by EPP and adjuvant RT for locally advanced MPM to assess feasibility. Patients with T3—4 or N2 MPM by CT and PET scans were enrolled on a phase II study. Induction therapy was: gemcitabine (1250 mg/m^2 days 1, 8) and cisplatin (75 mg/m^2 day 8) $\times$ 2—4 cycles. Patients underwent EPP 3—5 weeks after induction therapy, then 54 Gy RT 4—6 weeks postop. At surgery, 8/9 had complete resection by EPP with no postoperative deaths. All received planned adjuvant RT. This combined modality approach is feasible for locally advanced MPM, and initial analysis suggests improved resectability. This experience supports additional studies of induction and multimodality therapy, especially with regimens such as cisplatin and pemetrexed which may be better tolerated and more effective.

1. Introduction

There is no standard therapy for malignant mesothelioma of the pleura (MPM). Various series have reported median survivals of 4 to 12 months following diagnosis [1,2]. Studies evaluating the efficacy of single-modality treatment, chemotherapy, radiotherapy, or surgery have not consistently demonstrated a survival benefit [3]. Combined modalities such as surgery followed by adjuvant chemotherapy and radiotherapy have had limited success in only a highly select group of patients [4,5]. Relatively few patients have benefited from combined modality treatment because most patients present with unresectable disease. In

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addition, 20—25% of locally advanced MPM are found to be unresectable at the time of thoracotomy [6]. It is important to investigate new approaches to malignant pleural mesothelioma to improve its dismal prognosis.

1.1. Initial experience

One of the earliest large studies reported on 170 patients treated at a single institution from 1939 to 1981 [7]. This series included 102 epithelioid, 47 sarcomatoid, and 21 benign histologies. The surgical procedure of choice was pleurectomy; additional therapy included chemotherapy with cyclophosphamide and Adriamycin and radiotherapy with external beam or I^{125} seeds. This study distinguished benign or solitary fibrous tumors as a separate entity from malignant pleural mesothelioma and demonstrated a survival difference of 21 months versus 12 months for epithelioid and sarcomatoid histologies, respectively. The majority of patients died of local disease. No tumors were classified as mixed, and mesothelioma remained a diagnostic dilemma.

1.2. Brachytherapy and external beam radiotherapy

Because the majority of patients died of local disease, from 1976 to 1988 a trial evaluating the role of brachytherapy and external beam radiotherapy was conducted. This study enrolled 41 patients who had resection of all gross disease by pleurectomy to external beam radiotherapy alone and 54 patients with residual gross disease at the time of pleurectomy to brachytherapy with ^{192}Ir or ^{32}P followed by external beam radiotherapy [8]. Patients with radioactive seed implants had a median survival of 9.9 months compared to a 22.5-month median survival for patients without radioactive seeds. The difference in survival is probably explained by the residual gross disease remaining in the radioactive implant group rather than due to the differences in treatment, thereby stressing the importance of complete resection for prolonged survival benefit.

1.3. Role of extrapleural pneumonectomy

Since the value of complete resection of all gross disease appeared critical in providing prolonged survival, from 1985 to 1988, the lung cancer study group conducted a multi-institutional trial to evaluate the role of extrapleural pneumonectomy in the treatment of malignant pleural mesothelioma [9]. The study enrolled 83 patients with potentially resectable disease by CT scan; 20 patients underwent extrapleural pneumonectomy, 26 underwent pleurectomy decortication, and 37 had limited or no resection. Extrapleural pneumonectomy had the best median survival of 14 months, compared to 10 months for pleurectomy/decortication and 7 months for no resection. The conclusion of this trial was that extrapleural pneumonectomy was best at providing local control but more patients developed systemic disease.

1.4. Intrapleural cisplatin

At this point in time extrapleural pneumonectomy was still associated with a significant mortality, approximately 15%. Therefore, research efforts focused on pleurectomy followed by intrapleural chemotherapy to try to improve local control. From 1989 to 1992, 36 patients were enrolled, 28 patients had pleurectomy and intrapleural cisplatin 100 mg/m^2 and mitomycin 8 mg/m^2, 23 patients had intrapleural and systemic chemotherapy, extrapleurals were excluded but were still performed on patients with more advanced disease [10]. Median survival was 17 months, however there was serious toxicity associated with this regimen, and local control remained the problem in 80% of cases.

1.5. Staging

In 1995, a major contribution to the field of mesothelioma was the development of a universally accepted staging system that is currently accepted by the AJCC and the UICC. Now patients could be evaluated properly in a clinical trial setting and stratified by survival [11]. In 1999, this staging system was validated in a cohort of 231 patients demonstrating a median survival of 30 months for stage I, 19 months for stage II, 10 months for stage III, and 8 months for stage IV [12]. Advanced T status, advanced N status, and non-epithelioid histology were identified as poor prognostic factors. Mortality for extrapleural pneumonectomy in this cohort was 5%.

1.6. Local control

Therefore, given the improved operative mortality with extrapleural pneumonectomy, in 2001, a phase II trial using extrapleural pneumonectomy followed by high dose external beam radiotherapy at a dose of 54cGy, a dose which had never been previously administered, was conducted in 54 patients [4]. Stages I and II had a median survival of 33.8 months and stages III and IV had a median