ORIGINAL ARTICLE

Contemporary Analysis of Prognostic Factors in Patients with Unresectable Malignant Pleural Mesothelioma

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ABSTRACT

Introduction: Previous prognostic scoring systems for malignant pleural mesothelioma (MPM) included patients managed surgically and predated the use of pemetrexed. We analyzed prognostic factors in a contemporary cohort of patients with unresectable MPM who received pemetrexed-based chemotherapy.

Methods: This single-institution analysis included patients with MPM who were managed nonsurgically from 2000 to 2013. Variables correlated with overall survival (OS) included sex, performance status (PS), asbestos exposure, tumor laterality, histology, clinical stage, initial positron emission tomography maximum standardized uptake value, hemoglobin level, platelet count, lymphocyte count, white cell and neutrophil counts, treatment type, and clinical benefit from treatment. OS was analyzed by the Kaplan-Meier method, and significance ($p < 0.05$) of prognostic factors was analyzed by the log-rank test and Cox regression.

Results: A total of 191 patients met the study criteria: median age 71 years (range 46–90), 147 men (77%), 128 epithelioid tumors (67%), and 157 cases of stage III or IV MPM (82%). Median OS for all patients was 13.4 months. According to a univariate analysis, histology ($p < 0.001$), platelet count ($\leq$450,000 versus $>$450,000, $p < 0.001$), initial PS (0–1 versus $\geq$2), maximum standardized uptake value ($\leq$8.1 versus $>$8.1, $p = 0.037$), and lymphocyte counts ($p = 0.019$) were associated with OS. According to a multivariable analysis, only histology, platelet count, and PS were independent prognostic factors. Epithelioid histology, PS, and elevated lymphocyte count at diagnosis were significantly associated with clinical benefit from first-line chemotherapy.

Conclusions: Our results confirm the significance of elements of the Cancer and Leukemia Group B and European Organisation for Research and Treatment of Cancer prognostic scoring systems, identify factors associated with clinical benefit from chemotherapy, and emphasize the impact of histology and clinical benefit of chemotherapy on outcomes.

Keywords: Prognostic factors; Malignant mesothelioma; Pemetrexed; CALGB scoring system; EORTC scoring system

Introduction

Malignant pleural mesothelioma (MPM) is a rare tumor arising from the mesothelial cells of the pleura and is often related to asbestos exposure. The prognosis of MPM is poor, with a median survival of 9 to 12 months from diagnosis.[1] Chemotherapy alone for advanced stages, or in combination with surgery and/or radiotherapy for resectable disease, is the mainstay of treatment. For many patients with locally advanced disease that is not surgically resectable because of tumor invading the chest wall or the mediastinal structures,

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treatment options are limited to palliative chemotherapy, radiotherapy, or best supportive care alone. Since 2003, the combination of pemetrexed and cisplatin has been the standard first-line treatment based on the results of a phase III trial showing almost a 3 month improvement in median survival over treatment with cisplatin alone.[2] Chemotherapy beyond first-line treatment has no proven benefit.[3]

Various prognostic factors for survival in MPM have been described. The most significant prognostic factor remains histology: epithelioid mesothelioma is the subtype with the best prognosis.[4–7] The tumor, node, and metastasis staging system has been validated in several large series, but the radiological assessment of tumor extension is limited and can underestimate the real extent of the tumor.[5]

Two groups created prognostic scores to better select patients for more aggressive treatment: the Cancer and Leukemia Group B (CALGB) and the European Organisation for Research and Treatment of Cancer (EORTC).[4,8] The CALGB study included 309 patients who had a pathological diagnosis of mesothelioma and performance status (PS) of 0 to 2 and had participated in one of seven phase II trials between 1984 and 1994. Extent of pleural disease, lactate dehydrogenase level higher than 500 UI/L, poor PS, platelet count higher than 400,000, nonepithelial histology, and age older than 75 years were negative prognostic factors for survival. When only patients for whom all factors were available (195 of 309) were considered, pleural disease involvement and nonepithelial histology were not prognostic factors in a multivariate analysis. The best prognosis was in patients younger than 49 years and with a PS of 0.[4] The EORTC study analyzed 204 patients who were enrolled in five clinical trials between 1984 and 1993 and had a proven diagnosis of mesothelioma; the study found that white cell count (WBC), PS, certainty of histology, histological subtype, and sex were independent prognostic factors. Although both studies identified histology and performance status as the two main prognostic factors in patients with mesothelioma, these analyses included patients with a range of tumor stages at diagnosis, the majority of whom underwent major surgery and whose treatment predated the use of pemetrexed. Since the routine use of pemetrexed as first-line therapy began, only one new prognostic index for overall survival (OS) has been created; it is based on a retrospective analysis of 283 patients who were treated with chemotherapy alone in a clinical setting between 2007 and 2013. Histology, PS, stage (I–III versus IV), and pemetrexed-based chemotherapy were independent prognostic factors for survival; however, no factors were analyzed for association with clinical benefit from chemotherapy.[8] We therefore undertook this study to identify prognostic factors in a more uniform, contemporary cohort of nonsurgical patients treated with pemetrexed-based regimens, as well as to identify factors that might correlate with clinical benefit from chemotherapy.

Methods

Data Collection

We conducted a retrospective analysis of the medical records of patients with pathologically confirmed MPM who underwent evaluation and treatment between January 2000 and December 2013 at Memorial Sloan Kettering Cancer Center (MSKCC). Patients with peritoneal mesothelioma, patients treated at another hospital, and patients lost to follow-up were excluded. Patients who underwent pleurectomy with decortication or extrapleural pneumonectomy were excluded, although patients who had a surgical procedure for staging or diagnostic purposes or for palliation of a pleural effusion were included. Patients who had unresectable tumors at the time of surgery were also included (Fig. 1).

Clinical records were analyzed for the following: patient sex and age, documented exposure to asbestos, history of smoking, method of diagnosis (computed tomography [CT]-guided biopsy, surgical pleural biopsy, or cytologic analysis), site of disease, performance status (European Cooperative Oncology Group [ECOG] scale), blood count at the time of the first consultation, side of disease, clinical staging, maximum standardized uptake value (SUVmax) on positron emission tomography (PET) before the treatment, histological subtype (epithelioid, biphasic, or sarcomatoid), type of treatment (chemotherapy and/or radiotherapy or supportive care), chemotherapeutic agents, number of cycles and numbers of different chemotherapy regimens, and whether an exploratory thoracotomy had been performed. All tumor specimens were centrally reviewed by an MSKCC pathologist to confirm the diagnosis and histological subtype. All initial PET scans were performed before treatment but at varying times after diagnosis, and some were performed after talc pleurodesis.

Laboratory values used in the study were collected at the time of the first consultation at MSKCC. The normal ranges of values for hemoglobin level, platelet count, WBC, neutrophil count, and lymphocyte count were 13 to 17 g/dL, 160,000 to 400,000 per microliter, 4000 to 11,000 per microliter, 1500 to 8800 per microliter, and 500 to 5300 per microliter, respectively. For lymphocyte counts, the median in this cohort was used as a cutoff. For WBC and neutrophil count, the upper limit of normal was used as a cutoff.

Some patients in this analysis responded to induction chemotherapy or were considered clinically to have