A New Prognostic Score Supporting Treatment Allocation for Multimodality Therapy for Malignant Pleural Mesothelioma

A Review of 12 Years' Experience

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Introduction: Treatment of malignant pleural mesothelioma (MPM) remains a clinical challenge. The aim of this study was to identify selection factors for allocation of MPM patients to multimodal therapy based on survival data from 12 years of experience.

Methods: Eligible patients had MPM of all histological subtypes with clinical stage T1–3 N0–2 M0. Induction chemotherapy consisted of cisplatin/gemcitabine (cis/gem) or cisplatin/pemetrexed (cis/pem), followed by extrapleural pneumonectomy (EPP). Multivariate analysis was performed to assess independent prognosticators for overall survival (OS). A Multimodality Prognostic Score was developed based on clinical variables available before surgery.

Results: From May 1999 to August 2011, 186 MPM patients were intended to be treated with induction chemotherapy followed by EPP. Hematologic toxicity was significantly less frequent after cis/pem compared to cis/gem, but there was no difference in response or OS between the regimens. One hundred and twenty-eight patients underwent EPP with a 30-day mortality of 4.7%. Fifty-two percent of the patients received adjuvant radiotherapy. The median OS of patients undergoing EPP was significantly longer with 22 months (95% confidence interval: 20–24) when compared to 11 months (9–12) for patients treated without EPP. A prognostic score was defined considering tumor volume, histology, C-reactive protein level, and response to chemotherapy that identified patient groups not benefitting from multimodality treatment which was confirmed in an independent cohort.

Conclusion: Patients receiving induction chemotherapy followed by EPP for MPM of all histological subtypes and irrespective of nodal status showed a median survival of 22 months. A prognostic score is proposed to help patient allocation for surgery after validation in an independent cohort.

Key Words: Extrapleural pneumonectomy, Induction chemotherapy, Selection score, Malignant pleural mesothelioma, Multimodality therapy

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Treatment of malignant pleural mesothelioma (MPM) patients continues to be a clinical challenge. Advances over the last decades, including better understanding of tumor biology and improved quality of complete macroscopic resection, have changed the sceptical attitude toward this disease. This is a result of rising experiences with multimodality (MM) treatment strategies associated with a median survival up to 59 months in selected patients.[1–4] One of the most challenging questions is the selection of patients for aggressive treatment, considering the limited prognosis of MPM patients in general. To identify patient subgroups not benefitting from MM therapy and therefore to exclude those from surgery would be desirable.

In this article, we analyzed one of the largest series of consecutively treated patients with induction chemotherapy (cis/gem or cis/pem) followed by extrapleural pneumonectomy (EPP). We decided to establish a new Multimodality Prognostic Score (MMPS) using clinical variables for the decision to perform surgery.

PATIENTS AND METHODS

Patients and Indications

MPM patients treated at the Division of Thoracic Surgery of the University Hospital Zurich between May 1999 and August 2011 were analyzed. Eligibility criteria were biopsy proven MPM of any histological subtype, clinical stage T1–3, N0–2, M0 disease,[5] and resectability based on the decision of an interdisciplinary tumor board including a thoracic surgeon. Other inclusion criteria were as described previously.[2] For

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staging procedures, patients underwent computed tomography (CT) scan of the chest and/or positron emission tomography-CT scan before and after chemotherapy. In 81% of patients, videomediastinoscopy was performed for mediastinal staging to rule out N3 disease. Patients treated as part of the SAKK multicenter study (SAKK 17/04; ClinicalTrials.gov Identifier: NCT00334594; n = 45) are also included in the analysis. The treatment protocol was performed in compliance with the principles of good clinical practice, the Helsinki declaration, and institutional guidelines.

Treatment Plan

Induction chemotherapy consisted of three cycles of cisplatin and gemcitabine (cis/gem) or since March 2003 of cisplatin and pemetrexed (cis/pem) as described previously.[6]

Surgery (EPP) was performed within 6 weeks after completion of the last cycle of chemotherapy as described previously.[6] Final pathological staging was carried out following the tumor, node, metastasis (TNM) staging system.[7]

Radiotherapy was performed according to definite tumor stage and if high-risk zones were defined by the operating surgeon or according to SAKK 17/04 treatment protocol. Different radiation techniques and doses were applied over the years (3D-conformal radiotherapy and intensity-modulated radiation therapy [IMRT]). Overall 67 patients (52%) received adjuvant radiotherapy (12 patients in IMRT technique) after induction chemotherapy and EPP.

Analysis of Data

Data were collected from medical records archived in our data management program KISIM Version 4.816 (retrospective analysis 1999–2004, prospective documentation since 2004).

All consecutive patients intended to be treated with induction chemotherapy and EPP were retrospectively analyzed for toxicity of chemotherapy and survival. Toxicities assessed were grade III/IV hematological toxicity, grade III/IV nephrotoxicity, and unscheduled hospitalizations because of chemotherapy.

Response to chemotherapy was evaluated by modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria by one independent observer (T.F.)[8] in 128 cases with available prechemotherapy and postchemotherapy imaging as was the tumor volume (T.F. and D.N.-K.), which was assessed by the help of a semiautomated dedicated software (Myrian; Intrasense, Paris, France) as described previously.[9]

Patients undergoing EPP after induction chemotherapy were evaluated for putative prognostic factors for overall survival (OS) according to Simms et al.[10] Continuous variables were dichotomized by data driven approaches. The putative factors described for an association with outcome were sex, age (≤61 versus >61 years), exposure to asbestos, smoking, weight loss (≥10% body weight), chest pain, Eastern Cooperative Oncology Group performance status (0 versus 1 versus 2), white blood cell count (≤9.6 versus >9.6 G/liter), platelets count (≤400 versus >400 G/ liter), hemoglobin amount (≤117 versus >117 g/liter), C-reactive protein (CRP) level (≤30 versus >30 mg/liter), lactate dehydrogenase (≤480 versus >480 U/liter), cN2 assessed by mediastinoscopy, prechemotherapy histology and definitive histology (epithelioid versus nonepithelioid), extend of resection (R0/1 versus R2), RECIST factor (partial remission [PR] or stable disease [SD] versus progressive disease [PD]), tumor volume prechemotherapy and postchemotherapy (≤500 versus >500 ml), ypT stage, nodal status (ypN0 versus ypN1/2), lymph node ratio (positive lymph nodes: regional and mediastinal/ all resected lymph nodes), trocar infiltration, International Mesothelioma Interest Group (IMIG)-stages, regimen of chemotherapy (cis/gem versus cis/pem), radiotherapy (adjuvant radiotherapy versus no adjuvant radiotherapy), and European Organization for Research and Treatment of Cancer-classification (EORTC) score.[11]

Statistical analysis was carried out using the software package SPSS for Windows, 20.0.0 (SPSS Inc., Chicago, IL). Categorical data are given as total number and percentages and were compared between groups using Fisher's exact test. Continuous data are given as median with range.

Median survival time was assessed by Kaplan–Meier curves, and the influence of the different prognostic factors was analyzed by log rank-test. Survival time was calculated as time between application of the first cycle of chemotherapy and time point of death or last follow-up. For comparison of continuous variables in two independent groups, we used the Mann–Whitney U test.

Two-sided p values lower than 0.05 were considered statistically significant. To study the joint influence of the different factors on survival in a multivariate analysis, a stepwise Cox regression was performed including all prognostic factors being significant in the univariate analysis excepting factors being represented already in the score.

Based on our clinical experience, results from the literature,[12,13] and prognosis relevant factors derived from our survival analyses, we established a new MMPS to identify subgroups of patients not benefitting from MM therapy. The score contains four items with a maximum possible score of 4 if the patient presented all four conditions and 0 if none were present: tumor volume before chemotherapy was greater than 500 ml, nonepithelioid histological subtype in the diagnostic biopsy before chemotherapy, CRP value was greater than 30 mg/liter before chemotherapy, and PD after chemotherapy. A second score using the same variables without PD after chemotherapy was tested to evaluate factors being available at initial patient evaluation.

The predictive power of our new MMPS was compared with the existing EORTC score at 1 and 2 years using time-dependent receiver operating characteristic (ROC) curve estimation using the R package time ROC (version 0.2).[14] The prognostic impact of MMPS was further evaluated in the intention to treat (ITT) cohort without surgery (n = 37) and in an independent cohort of patients treated at the Division of Thoracic Surgery, University Hospital in Vienna (n = 22) with the same treatment approach of induction chemotherapy followed by EPP.

RESULTS

From May 1, 1999 until August 2011, 186 out of 323 MPM patients were eligible and agreed to undergo induction chemotherapy followed by EPP (ITT group): the initial

