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An overview of neoadjuvant chemotherapy in the multimodality treatment of malignant pleural mesothelioma

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ABSTRACT

Malignant Pleural Mesothelioma (MPM) is an aggressive tumour with poor prognosis and increasing incidence in industrialized countries because of the previous widespread exposure to asbestos fibres and to the long lag period from time of exposure and the diagnosis of the disease.

MPM shows high refractoriety to systemic treatment, single-modality treatment was generally ineffective and did not achieve higher results than supportive care.

The incidence of local and distant recurrences after surgery remains high and that was the reason for many centres to perform combined treatments. In the attempt of reducing the incidence of local recurrences, a multimodality approach with surgery followed by adjuvant radiotherapy was explored. Extrapleural pneumonectomy (EPP) allows higher doses of radiotherapy to the whole hemithorax by avoiding pulmonary toxicity and the results of this approach is a significant reduction of loco-regional relapses; although, extrathoracic metastasis represent a major problem in the management of the disease because of the impact on overall survival. The success with surgical resection after neoadjuvant chemotherapy in stage IIIA lung cancer has been the impetus for several groups to apply this strategy in MPM aiming at reducing the incidence of distant relapse after surgery.

Platinum-based chemotherapy plus gemcitabine or pemetrexed for 3–4 cycles followed by surgery and postoperative high-dose radiotherapy showed the best results in terms of overall and progression free survival.

This review will focus on the main clinical studies and overview the results of different chemotherapy regimens in the neoadjuvant treatment of MPM.

Introduction

Malignant pleural mesothelioma (MPM) is a rare and aggressive tumour with a poor prognosis and increasing incidence and mortality in the next fifteen years because of the long lag time (even 40 years) from exposure to clinical evidence.[1]

The management of the disease is still controversial; single-modality treatment generally did not achieve higher results than supportive care.

MPM shows high refractoriety to systemic treatment, responses are of short duration and complete responses are rarely observed.

Currently available chemotherapy regimens achieved a response rate of 30–40%, a median progression free and overall survival of approximately 6 and 12 months respectively.[2,3]

Extrapleural pneumonectomy (EPP), a surgical procedure introduced in the seventies which implies en bloc resection of the parietal pleurae, lung, ipsilateral pericardium and hemidiaphragm, did not improve the incidence of local and distant recurrences and that was the reason for some centres to conceive combined treatments.

In the attempt of reducing the incidence of local recurrences after extrapleural pneumonectomy, a multimodality approach with surgery followed by postoperative radiotherapy was explored.

Extrapleural pneumonectomy allows higher doses of radiotherapy to the whole hemithorax by avoiding pulmonary toxicity and the result of this approach is a significant reduction of loco-regional relapses.[4]

The issue of extrathoracic metastasis represents a major challenge in the management of the disease because of the impact on overall survival.[5]

Once a chemotherapy regimen shows activity in advanced malignant pleural mesothelioma, a subsequent step was the addition of such treatment to surgery and radiotherapy to improve the systemic control of the disease.

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The success with surgical resection after neoadjuvant chemotherapy in stage IIIA non-small cell lung cancer has been the impetus for several groups to apply this strategy in malignant mesothelioma aiming at reducing the incidence of distant relapse.[6,7]

As well as in non-small cell lung cancer, neoadjuvant chemotherapy could maximize cytoreduction and increase the proportion of patients able to complete the following treatments.

Furthermore, the difficult administration of both postoperative chemotherapy and radiotherapy in most patients induced many groups to introduce a trimodality approach based on preoperative chemotherapy, surgery and postoperative radiotherapy in the attempt of improving compliance.

This review offers an overview of the clinical trials about neoadjuvant chemotherapy within a trimodality approach of malignant pleural mesothelioma.

Search strategy

Electronic search was performed using PubMed and the Cochrane database. To optimize the search strategy we used the terms *mesothelioma* and *neoadjuvant chemotherapy*.

We also reviewed the reference lists in relevant publications and the abstracts from the meetings of the American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), European Multidisciplinary Cancer Congress (ECCO), International Association for the Study of Lung Cancer (IASLC) and International Mesothelioma Interest Group (IMIG) were also examined.

Doublet chemotherapy with gemcitabine plus a platinum compound

Since the end of the nineties, several groups analyzed the effectiveness and toxicity of gemcitabine combined to carboplatin or cisplatin in advanced mesothelioma patients.[8–12]

Those phase II trials showed a response rate ranging from 12% to 47%, an overall survival from 10 to 16 months, and a progression free survival from 6 to 10 months.

In the wake of the results by Byrne in the setting of metastatic disease, in 2004 a Swiss group conducted a pilot study investigating neoadjuvant chemotherapy with cisplatin and gemcitabine followed by extrapleural pneumonectomy with or without adjuvant radiotherapy in 19 malignant pleural mesothelioma patients with resectable disease.[13]

Induction chemotherapy consisted on three cycles of cisplatin 80 mg/m^2 on day 1 *plus* gemcitabine 1000 mg/m^2 on day 1, 8, 15 every four weeks.

Extrapleural pneumonectomy was planned in all patients, while the total dose and fractionation of radiotherapy was decided according to resection margins and the target volume (hemithoracic three-dimensional conformal radiotherapy 30–60 Gy). 13 (68%) patients completed the entire trimodality treatment.

Response rate to neoadjuvant chemotherapy was 32%; median overall survival in the intention-to-treat population was 23 months; disease free survival in patients who received preoperative chemotherapy and extrapleural pneumonectomy was 16.5 months.

The authors observed a higher compliance to neoadjuvant compared to the adjuvant chemotherapy; in fact, the three cycles of chemotherapy were administered successfully in 95% of the patients.

The preoperative systemic approach did not increase perioperative mortality rate, and the morbidity rate was in line with previous experience.

The good toxicity profile of chemotherapy regimen and the efficacy and activity results suggested further investigation of such treatment in a Swiss multicenter study.[14]

The study investigated the feasibility of three cycles of cisplatin *plus* gemcitabine at the same doses previously adopted, followed by extrapleural pneumonectomy and adjuvant radiotherapy up to 60 Gray to the involved hemithorax, in 61 patients. Quality of life assessment was one of the endpoints of the study.

Chemotherapy was administered to 95% of the patients, while the resection rate was 74%. Complete resection (R0–R1) was achieved in 37 (61%) of the 45 patients who underwent EPP.

Trimodality treatment was completed by 36 (59%) patients, with an overall survival of 19.8 months in the intention-to-treat analysis and 23 months in patients who received both chemotherapy and surgery with or without adjuvant radiotherapy.

Median time to progression was 13.5 months, while no radiologic response rate was reported in the study. No significant worsening of quality of life was showed during the multimodality treatment. The postoperative mortality (2.2%) and the morbidity rate (35%) were acceptable and underline the need for experienced centre to perform such approach.

Considering the risk of increasing perioperative complications and postoperative mortality with the use of neoadjuvant chemotherapy, the administration of a chemotherapy regimen with lower toxicity seemed attractive.

Since 1996, our Italian group tested the activity of carboplatin plus gemcitabine in a phase II study in 50 mesothelioma patients.[10] We observed partial response in 26% of the patients, a median overall survival and progression free survival of about 16 and 10 months, and an acceptable toxicity profile.

Those results led us to evaluate the same chemotherapy combination in the neoadjuvant setting of a multimodality approach in 21 patients with resectable disease.[15] Patients with stage I to III, epithelial or mixed mesothelioma underwent three to four cycles of chemotherapy with carboplatin area under the concentration–time curve (AUC) 5 on day 1 and gemcitabine 1000 mg/m^2 on days 1,8,15 every four weeks. Patients with complete or partial response or stable disease underwent extrapleural pneumonectomy within 4–6 weeks. Postoperative radiotherapy consisted of 45 Gy in 25 fractions to the hemithorax, with a boost dose of 10–14 Gy to high risk areas.

At the reassessment after induction chemotherapy, we observed 7 (33.3%) partial response and 14 (66.7%) stable disease.

The operability rate was about 81%, and 71% of the patients completed the trimodality protocol. The median overall survival was 25.5 months in the intention-to-treat population, and 27.5 months in patients who received extrapleural pneumonectomy. Median time to relapse was 16.3 months. No intraoperative or perioperative morbidity was shown, while major complications were observed in 23.8% of the operated patients.

The absence of postoperative mortality characterizes another prospective study, conducted at the Memorial Sloan-Kettering Cancer Center.[16]

From 2002 to 2004, 21 patients with locally advanced mesothelioma (stage III-IV) were entered into a phase II trial designed to test the feasibility of induction chemotherapy with cisplatin and gemcitabine followed by extrapleural pneumonectomy and external beam hemithoracic radiotherapy (EBRT). Chemotherapy included 4 cycles of gemcitabine 1250 mg/m^2 on days 1,8 combined with cisplatin 75 mg/m^2 on day 1 every 21 days. Extrapleural pneumonectomy was performed within 3–5 weeks, in those patients who had resectable disease, followed by EBRT 54 Gy/30F starting 3–6 weeks after surgery.

Nineteen patients started chemotherapy and 53% of them completed 4 cycles. 8 patients underwent EPP followed by EBRT, with 42% of patients who completed the trimodality treatment. Response to chemotherapy were: 26% partial response, 32% stable disease, 42% progressive disease.