Mesothelioma treatment: Making the proper choice

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Introduction

Malignant mesothelioma (MM) is a nearly invariably lethal tumour of the pleura or peritoneum whose origin is closely linked to the exposure of asbestos fibres [1]. Survival of the treated patients is dismal with a median of less than 12 month after diagnosis. However, some long term survivors have been identified. In most cases they are predicted by histological subtype, performance score, thrombocyte count and extent of disease at time of diagnosis [2].

MM is notoriously refractory to the different treatment modalities available. Neither surgery nor radiotherapy alone has resulted in increased survival. Only in patients with a very limited stage have long term survivors been found.

Chemotherapy has been tested using either single agents or combination regimens. Response rates of 14 to 40% with a small improvement in median survival have been reported in most phase II trials [3–5].

Although some chemotherapy regimens like high dose methotrexate and doxorubicin or gemcitabine and cisplatin give a hint of improved survival and response rate, nearly all tumours recur within 2 years. One of the most recent improvements in treating patients is the use of pemetrexed. Pemetrexed is a multi-target antifolate which exerts its action by blocking three different enzymes that are involved in the folate metabolism (GARFT, TS and DHFR). Although its action as a single agent is limited to 14% [6] it is active in combination with a platinum compound. Data on the combination of carboplatin and pemetrexed have been promising [7] and a large phase III study, comparing cisplatin versus cisplatin with pemetrexed has shown a significant improvement in response rate, median survival and quality of life [8]. A comparable study tested the efficacy of raltitrexed plus cisplatin versus cisplatin alone and showed similar results [9]. Close analysis of these data reveal that the achieved advantage of 2–3 months cannot be maintained for 2 years or longer. Therefore, it is imperative that new therapeutic approaches are explored in order to maintain an improved response and survival.

One of the important targets in cancer therapy and also in malignant mesothelioma is the vasculature. It is well understood that inhibition of vascular growth factors and angiogenetic compounds could play an important role in further management of this disease. Although it is not expected that the use of these factors will completely eradicate tumours, it is hoped they can inhibit progression of growth. Malignant mesothelioma cells often express vascular endothelial growth factor (VEGF) and to some extent basic fibroblast growth factor (b-FGF) [10,11]. Currently, a study has reported on the positive effects of the addition of bevacizumab to a standard regimen of cisplatin and gemcitabin [12].

Whom to select for which therapy?

As indicated earlier, there is no real role for surgery or radiotherapy alone. However, new studies have been performed in which patients have received induction chemotherapy followed by radial resection and radiation. This multimodality approach is very demanding and difficult to tolerate for the patient. For this type of experimental therapy only very fit patients with good cardio-pulmonary reserves and with low volumes of tumour load are selected. One of the important selection criteria is shrinkage of the afflicted site of the thorax. This clinical and radiological sign indicates a progressive sclerosis of the thoracic cavity and surgery then becomes very difficult. In general, the first modality of treatment is chemotherapy which is quite well tolerated (Fig. 1). The second step is the surgical resection which implies the removal of all pleural lining, diaphragm, part of the pericardium and often the whole lung. Improvements in anaesthetic methods and the skill of the operating team in the specialised centres have reduced the post-operative mortality to <3%. The Extra Pleural Pneumonectomy (EPP) approach carries a significant morbidity with infectious disease and cardiac rhythm disorders are frequent side effects. As a final treatment modality, radiation is applied with dosages of >50 Gy to the

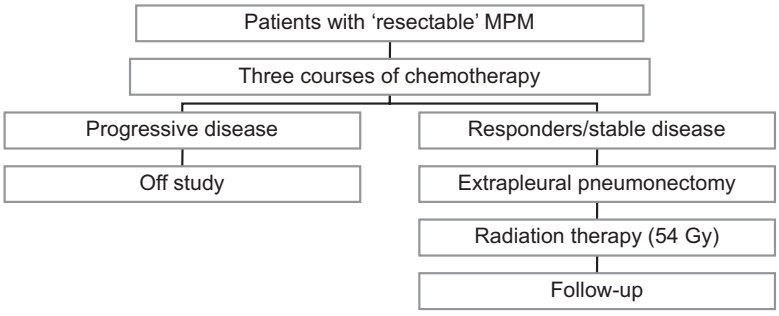

Fig. 1. Flow chart of EORTC study 08931.

entire hemithorax. In general, co-planar fields are applied but also Intensity Modulated Radiotherapy (IMRT) is considered. Due to the large volume of irradiation, side effects occur like fatigue, oesophagitis and pneumonitis can occur.

Long term follow-up of this approach has scarcely been reported and it is clear that for the majority of patients this approach is not feasible. For the patients with reasonable performance, classical chemotherapy of an antifolate with a platinum compound should first be considered. Depending on confirmatory studies with angiogenesis inhibitors, these drugs can be co-administered during or after the treatment. In the near future new studies will test the efficacy of new drugs such as thalidomide, zactima, sunitinib, sorafenib, etc.

For second line treatment no standard of care has yet been defined. Best supportive care, local radiation therapy and pain treatment should be given to patients when required, but chemotherapy may also be considered [13]. Testing of new drugs in second line is only indicated as part of a study protocol.

Conflict of interest statement

None declared.

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