Editorial

Improvement of Malignant Pleural Mesothelioma Prognosis: Early Diagnosis and Multimodality Treatment

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Malignant pleural mesothelioma (MPM) is the most common primary malignancy of the pleura. The occurrence of malignant mesothelioma is typically related to exposure to mineral fibers such as asbestos and erionite.[1-3] Reports suggest that genetic factors may also play a role in MPM.[4] Moreover, latency periods that are the period of time between the first exposure to asbestos and a disease diagnosis range from 20 to 50 years. The mortality burden from asbestos-related diseases (ARD) is heavy and ARD accounts for 92,250 deaths per year globally.[5] To improve survival of MPM patients, effective strategy of early diagnosis and effective treatment strategies are highly needed.

Early Diagnosis of Malignant Pleural Mesothelioma

Early diagnosis of the MPM is in favor of patients' survivals; medical thoracoscopy (MT) is beneficial for early diagnosis.[6] Because the onset of MPM is insidious, most patients have advanced disease at presentation. Initial clinical and radiological examination usually reveals a pleural effusion. The diagnosis of MPM can be difficult, with symptoms and clinical findings that can mimic and be mimicked by other diseases. The differential diagnosis of pleural effusions can present a considerable challenge. After thoracocentesis and/or blind pleural biopsy, about 25–40% of the pleural effusions remain undiagnosed.[7] Thoracoscopy-guided biopsies have high sensitivity and low complication rates with a diagnostic yield of about 80–90% (or more) for MPM. Standard video-assistant thorascope-guided biopsy is suitable for other patients with a pleural effusion, or patients for whom surgical pleurodesis is considered.[8] MT has been estimated an effective and safe procedure for diagnosing pleural effusions of undetermined causes. In the previous study, our data showed that the overall diagnostic efficiency of MT was 92.6% for pleural effusions of undetermined causes in a Chinese population.[9] MPM is a challenging disease to treat with a median survival of 9–17 months for all stages of disease and is often fatal in 4–8 months if untreated.[10] In our retrospective study, the survival time of 43.3% (13/30) patients was >12 months and 30% (9/30) patients was more than 17 months; of the thirty MPM patients, 25 were diagnosed through MT.[6] MT under local analgesia is used increasingly by respiratory physicians, with a diagnostic yield comparable to standard surgical VAT for early diagnose of a MPM.

Regimens of Chemotherapy

Chemotherapy alone is recommended for patients with performance status (PS) 0–2 who are not operable or refuse surgery, those with clinical Stage IV MPM, or those with sarcomatoid histology.[11] A combined first-line regimen using cisplatin/pemetrexed is considered the gold standard for MPM. A recent multicenter Phase 3 randomized trial compared adding bevacizumab to cisplatin/pemetrexed (with maintenance bevacizumab) versus cisplatin/pemetrexed alone for patients with unresectable MPM and PS 0–2 who did not have bleeding or thrombosis.[12] Overall survival

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was increased in the bevacizumab plus chemotherapy when compared with chemotherapy alone. The NCCN panel recommends (category 2A) bevacizumab, cisplatin, and pemetrexed for patients with unresectable MPM based on this trial.[11] There are no data to support optimal chemotherapy duration in MPM. In current practice, chemotherapy treatment is administered for a median of 4–6 cycles, unless progression or severe toxicity occurs.[13] Although a small study has shown that continuation of pemetrexed alone after induction with cisplatin and pemetrexed is feasible, there are no randomized trials supporting the efficacy of the maintenance approach.[14] We also find that chemotherapy with pemetrexed and cisplatin or carboplatin and continuation of pemetrexed alone could prolong the survival time of the patients.[6]

The second-line chemotherapy options include pemetrexed (if not administered first line), vinorelbine, or gemcitabine. After treated with vinorelbine and/or gemcitabine as second- or third-line therapy, 46% of patients had stable disease.[15] Combination chemotherapy using gemcitabine with vinorelbine was shown to achieve 82% disease control (stable disease + partial response + complete response) in 17 Japanese MPM patients pretreated with platinum plus pemetrexed chemotherapy.[16]

Controversial Surgery

The choice of surgery for MPM is controversial because data from randomized controlled trials are not available. Surgical resection for patients with MPM can include either (1) pleurectomy/decortication (P/D), which is complete removal of the involved pleura and all gross tumor; or (2) extrapleural pneumonectomy (EPP), which is *en bloc* resection of the involved pleura, lung, ipsilateral diaphragm, and often the pericardium. The fact is that 30-day mortality was too high in patients proceeded to EPP from 2.2% to 11% and the in-hospital mortality can reach 31%. However, P/D seems to be safer than EPP with 30-day mortality from 0% to 11% and P/D is associated with lower perioperative mortality and potentially better functional status. Although P/D may be safer than EPP, it is not clear which operation is oncologically better. Because of the diffuse growth pattern and the lack of surgical margins for MPM, microscopic complete resection is theoretically impossible. Patients with epithelial histology, a primary tumor that is limited in local extent and no nodal metastases, demonstrate the greatest survival benefit following surgical resection.[17]

Radiotherapy as a Subsidiary Role

Radiotherapy (RT) plays a subsidiary role in treatment of MPM. It can be used for different indications in mesothelioma: as palliation, as preventive treatment, and as a part of multimodality treatments. Currently, there is no convincing evidence in offering systematically RT for port-site prophylaxis.[13] The early study found that RT was effective in prophylactic irradiation in terms of tract-metastases free survival. Adjuvant irradiation after P/D is usually not recommended but may be considered with caution and under strict dose limits of organs at risk, only in the context of prospective clinical trials. There are no randomized data to support adjuvant post-EPP RT, but historical comparison suggests that RT at the total dose of 54 Gy could be associated with a significant reduction in local failure.[13] The best timing for delivering RT after surgical intervention and/or in conjunction with chemotherapy should be discussed in a multidisciplinary team, including radiation oncologists, surgeons, medical oncologists, diagnostic imaging specialists, and pulmonologists.[11] A role for palliative hypofractionated RT (daily doses of 3–5 Gy) for the control of secondary chest pain is proven. A careful clinical evaluation, however, is mandatory in every single patient, especially considering that such treatments may be associated with acute toxicities.[13]

Assessment of Prognosis

Prognosis assessment can explain variations in patient outcomes and help doctors make appropriate management recommendations for individuals. Factors such as histological type, neutrophil to lymphocyte ratio (NLR), soluble mesothelin-related peptide (SMRP), and quantitative 18-fluoro-deoxyglucose positron emission tomography (PET) techniques have been examined for disease progression and survival. MPM is classified into three histologic subtypes: epithelial, sarcomatoid, and mixed or biphasic. Patients with epithelioid histology have better outcomes than those with either mixed (biphasic) or sarcomatoid histologies.[18] NLR externally validated prognostic indices in a total of 171 MPM patients retrospective study.[19] High baseline SMRP serum levels are predictive of reduced mean survival in the epithelioid subtype.[8] Quantitative PET parameters, such as standardized uptake value (SUV) and total glycolytic volume (TGV) which is a composite of anatomical (tumour volume) and functional (SUV, metabolic activity) data to reflect total metabolically active tumor burden, are applied to provide prognostic information. In systematic reviews, a higher SUV is associated with shorter median survival from a number of studies. Moreover, higher baseline TGV is associated with shorter survival in patients scheduled to undergo chemotherapy.[20]

In conclusion, the efficacy of current therapies for MPM is, unfortunately, very limited, and the overall prognosis remains quite poor. To improve survival of MPM patients, the optimal management of MPM may be early diagnosis, multimodality treatment, and developing new treatment options, such as immunotherapy and targeted therapies directed against genomic abnormalities.

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