Chapter

Mesothelioma, a Review of Current Guidelines

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Abstract

Mesothelioma is considered as a rare tumor originating in the mesothelial surfaces of pleura or, more rarely, in other sites such as peritoneum, which harbors a very poor prognosis. Despite clinical research efforts, lack of available therapies remains clear. Standard of care treatments and guidelines have not been evolved much along recent years. In this chapter, main guidelines will be reviewed, besides a systematic Pubmed review, with a focus on epidemiology, diagnosis tests, and approved local and systemic treatments, including most important advances. Searched terms included "mesothelioma," "ESMO and NCCN guidelines," "diagnosis," "surgery," "targeted therapy," "clinical trials," "palliative treatment," and "meta-analysis." First-line regimen recommendations have not evolved since the phase III pivotal study of cisplatin-pemetrexed was published, and this combination became the standard of care. Targeted therapies have brought disappointing results. However, recent clinical trial data with immunotherapies are bringing some light and may become a new paradigm in the following years.

Keywords: malignant mesothelioma, chemotherapy, pemetrexed, immunotherapy, clinical trials, nivolumab, pembrolizumab, targeted therapy

1. Introduction

Malignant mesothelioma (MM) is a fatal disease which originates in the mesothelial surfaces of pleura or, more rarely, in other sites such as peritoneum. Most cases have been classically linked to asbestos exposure; however, ionizing radiation may also increase the risk of mesothelioma [1].

Its prognosis is very poor and it is difficult to treat, mainly because most patients are diagnosed with advanced disease [1–3]. Despite clinical research efforts, lack of available therapies remains clear and median overall survival is still approximately 1 year, with only 10% patients alive 5 years after diagnosis. Standard of care treatments and guidelines have not been evolved much along recent years. In this chapter, NCCN and ESMO guidelines have been reviewed, besides an electronic search of the Pubmed database, with a focus on the phase II and III clinical trials, guidelines, meta-analysis, and systematic reviews regarding epidemiology, diagnosis tests, surgical approach, and approved local and systemic treatments, including most important advances. Searched terms included "mesothelioma," "ESMO and NCCN guidelines," "diagnosis," "surgery," "targeted therapy," "clinical trials," "palliative treatment," and "meta-analysis." First-line regimen recommendations have not evolved since the phase III pivotal study of cisplatin-pemetrexed was published, and this combination became the standard of care despite its modest benefit

in survival. Pemetrexed seems to be the most active drug, but its use in the first-line setting limits its administration in further lines. However, a rechallenge may be done in responder patients, who might still get benefit [4].

Only few drugs have demonstrated a mild activity in refractory MM, and targeted therapies have provided disappointing results so far. However, recent clinical trial data with immunotherapies are bringing some light and may become a new paradigm in the following years.

2. Epidemiology

Malignant mesothelioma (MM) is a rare tumor, with an incidence of less than 5 out of 100,000 inhabitants in Europe [1]. Diagnosis is usually done when disease is well advanced, and patients have a high symptom burden [3]. Incidence has decreased along the last decades globally worldwide. Mesothelioma has been typically related to asbestos exposure, which is the most well-known risk factor, although the latency period can be long, with a latency period being approximately 40 years, although in some cases, it may be as long as 60–70 years. Recent reports have suggested that also ionizing radiation may have a role, such as in patients previously treated with radiotherapy (RT). Other studies also suggest that erionite (which may be found in travel roads) increases the risk of MM. Smoking is not a risk factor. There may be a genetic risk in patients with BRCA-1 mutation [5–7].

The most common type of mesothelioma is malignant pleural mesothelioma, being up to 70% cases, followed by peritoneal (30%) and pericardial mesothelioma (1–2%) [2]. According to histology, there are three subtypes: epithelial, sarcomatoid, and biphasic [3], with epithelial subtype having a better prognosis.

Prevalence is highly linked to mortality, and mesothelioma is an unmet medical need due to its very poor prognosis, having a median overall survival of approximately 9–12 months, with only very modest improvements in survival over time [8].

3. Diagnosis

Most common symptoms include dyspnea, thoracic pain, and weight loss. Usually unilateral effusions are observed. A detailed occupational history is key, checking asbestos exposure among other previously exposed potential risk factors. Patients often present with advanced disease, but without distant metastases, as local implants or effusion cause pain and/or dyspnea. Brain metastases are rare [3].

Diagnosis assessments include chest X-ray, computed tomography (CT) scan of chest and upper abdomen, and thoracentesis, with examination of the pleural effusion and general laboratory blood tests [1]. Citology samples from pleural effusion are frequently negative or inconclusive, hence, histology may bring some further light for a more accurate diagnosis. Some biomarkers may be helpful, including calretinin, WT-1, D2-40, and citokeratyn 5/6, being negative in mesothelioma and positive in lung adenocarcinoma [9]. In order to obtain adequate histology, a thoracoscopy is highly recommended to optimally stage and to allow pleural fluid evacuation (with or without pleurodesis) [9, 10]. Mesothelioma can be difficult to identify and distinguish from benign pleural lesions and from other malignancies; it is therefore recommended to obtain biopsies from the tissue of both abnormal and normal appearance. When a thoracoscopy is not feasible or contraindicated, ultrasound-guided true-cut biopsies are a good alternative [10].

4. Pathology

MM comprises a heterogeneous group of tumors, which are mainly classified as three subtypes (epithelioid, biphasic, and sarcomatoid), despite the numerous variants that are described in the 2004 WHO classification [9].

Diagnosis samples may be obtained from pleural effusions, pleural biopsies, and surgical samples [1, 8–10]. Cytological diagnosis from effusion samples may be feasible, but sensitivity is highly variant, with variable atypia (usually low grade). Therefore, usually tissue biopsies with immunohistochemistry analysis are pivotal for confirmatory diagnosis.

Standardly used and most recommended biomarkers for diagnosis include calretinin, cytokeratin 5/6, WT1, and podoplanin (D240). For non-small cell adcenocarcinoma, the most useful markers are TTF1, CEA, and EP4 [8].

5. Staging

Staging procedures are aimed to describe anatomical extent correlating with prognostic features, which is key in order to make treatment decisions. Standard procedures for staging include chest and abdomen CT with contrast and PET/CT (for those patients who may undergo surgery). Video-assisted thoracoscopy (VATS) is recommended if contralateral disease is suspected [3].

Patients should be evaluated by a multidisciplinary committee, including oncologist, radiation oncologist, pathologist, pulmonologist, diagnostic imaging specialist, and surgeon.

The limitation of most classifications is their inaccuracy in describing tumor (T-) and node (N-) extent. The most recent staging system was presented by the International Mesothelioma Interest Group (IMIG) [11]. However, it failed to be an independent prognostic factor when analyzed in the clinical setting using multivariate analysis [11–14]. Hence, further workup is needed in order to get an accurate and prognostic staging system.

If a surgical resection is planned, either mediastinoscopy or endobronchial ultrasound of mediastinal lymph nodes are recommended [15]. Besides, two additional tests may be useful if suggested by imaging: laparoscopy in order to rule out any transdiaphragmatic extension and chest MRI to check vascular involvement [14–17].

6. Treatment for mesothelioma

6.1 First-line therapy for mesothelioma

Chemotherapy is recommended as the sole therapy for patients with ECOG 0–2 who are not amenable for surgery. For patients with ECOG 3–4, best supportive care is strongly recommended.

Chemotherapy has a role in the palliative treatment of advanced mesothelioma, getting an improvement of symptoms and modest benefit in survival. Standard first-line treatment is based on platinum doublets, with either pemetrexed or raltitrexed [18, 19], being cisplatin/pemetrexed the only FDA-approved regimen. This combination was investigated in a phase III trial comparing cisplatin/pemetrexed vs. cisplatin monotherapy, getting a benefit in survival by 2.8 months (12.1 vs. 9.3 months, $P = 0.02$) [18].

Carboplatin may be used as an alternative to cisplatin, particularly in fragile patients, with no significant differences in survival and a better safety profile [20, 21].

Clinical research has been trying to look for an improvement with the addition of several agents; however, several phase II trials have failed to demonstrate improvement over standard treatment with the addition of antioangiogenics such as bevacizumab or sunitinib [22, 23]. However, a phase III trial compared cisplatin/pemetrexed with or without bevacizumab in patients who were suitable for receiving bevacizumab (ECOG 0–2 with no history of bleeding or thrombosis). Experimental arm was better in terms of survival, with a benefit by 2.7 months (18.8 vs. 16.1 months, P = 0.0167). Grade 3–4 adverse events were more common in the experimental arm, 71 vs. 62%, with more cases of hypertension, grade 3 proteinuria and grade 3–4 thromboembolic events in the bevacizumab arm. The NCCN guidelines then recommends cisplatin/pemetrexed plus bevacizumab followed by maintenance bevacizumab in patients without contraindications [24].

6.2 Second-line therapy for mesothelioma

There is a lack of treatment options in the second line and beyond setting, this being an important medical need with no standard of care yet. Pemetrexed as single agent when compared with the best supportive care was not able to provide an improvement in survival [25]. Vinorelbine showed a benefit in terms of responses in several small phase II trials [26].

Both immunotherapies and targeted therapies are under evaluation as well, but they have not been yielded into approval [27, 28]. In the absence of the standard second-line or further-line therapy, it is recommended that patients are enrolled into clinical trials. Recent data suggest that checkpoint inhibitors may have a role in this setting, with a response rate slightly higher than that previously obtained by other agents [3].

Checkpoint inhibitors target the programmed death-1 (PD-1) receptor, which improves tumor immunity. Both nivolumab and pembrolizumab target PD-1 receptors, but testing this receptor is not required [29].

6.3 Immunotherapy and targeted therapies

Some immunotherapies have been tested or are under clinical development for MPM, including antibodies blocking immune checkpoints that function as negative regulators of T-cell function, cytotoxic T-lymphocyte-associated antigen 4 (CTLA4), programmed death 1 (PD-1), and programmed death ligand 1 (PD-L1). However, there is still a lack of strong support for their use.

In two nonrandomized studies, the anti-CTLA4 antibody tremelimumab showed preliminary evidence of activity in patients with previously treated mesothelioma [28, 30]. Thereafter, a randomized, placebo-controlled study investigated tremelimumab in patients with mesothelioma (the DETERMINE trial). This trial did not meet the primary end point of OS, as we did not find statistically significant differences in OS between the tremelimumab group [median OS 7.7 months (95% CI: 6.8–8.9)] and the placebo group [median OS 7.3 months (95% CI: 5.9–8.7)] [31].

In the KEYNOTE-028 trial, previously treated patients with PD-L1-positive MPM received pembrolizumab 10 mg/kg every 2 weeks for up to 2 years or until confirmed progression or unacceptable toxicity. Five of 25 patients (20%) had a partial response (objective response rate of 20%) and 13 (52%) patients had stable disease. Additionally, there was a maintained clinical benefit, with a median duration of response 12.0 months (95% CI: 3.7 not reached) [32, 33]. The NivoMes

study, which evaluated nivolumab in unselected patients with previously treated mesothelioma reported response rates of 28%. The JAVELIN study of the anti-PDL-1 antibody avelumab in unselected patients with previously treated mesothelioma reported a response rate of 9.4% with a median PFS of 17.1 weeks. Subgroup analysis in the PD-L1-positive population (cutoff > 5%) showed a response rate of 14% [34]. Novel vaccine approaches using MPM neoantigens identified by gene sequencing are also entering clinical trial on the basis of early animal studies [33].

As a summary, preliminary data on PD-1- and PD-L1-targeting monoclonal antibodies in MPM suggest that immunotherapy with single agents may have some benefit, possibly because of its complex biology.

6.4 Radiotherapy

Administering RT to the entire pleural surface without damaging radiosensitive sites and keeping a good safety profile is very challenging. Radiotherapy (RT) is used in different settings as treatment for MM: palliative, adjuvant, and as part of a multimodality treatment.

As palliative treatment for pain relief bronchial obstruction or other disease related symptoms, there is no strong evidence to support its use; however, it may be recommended in cases of infiltration of the chest wall, administered in short courses such as 1 × 10 or 3 × 8 Gy [35], always understanding that dose of radiation should be based on its purpose.

6.4.1 Pre- and postoperative RT

Limited evidence is available, extracted from retrospective studies only. In general results are poor, in terms of disease control rate, because of the complex growth patterns of the disease. Furthermore, its safety profile is poor due to the wide field size and neighboring vital organs. The introduction of intensity-modulated RT (IMRT) seem to overcome most of these issues and allow the remaining tumor tissue to be properly irradiated. Preliminary results adjuvant IMRT seemed particularly promising. Further studies are needed to better establish the role of RT. Recent studies have underlined the importance of RT technique, both in terms of local control and toxicity. It is therefore recommended that RT is delivered in specialized centers (expert advice) [36, 37].

6.5 Surgery

Surgery may be recommended for patients with stage I to IIIA disease who are in good conditions and are medically operable. A careful assessment before proceeding to surgery is strongly recommended [1, 3].

Objectives of surgery are staging, palliative, and, more uncommonly, curative intent.

6.5.1 Surgery with radical intent

It cannot be considered to have a real radical intention, as its objective is actually obtaining a macroscopic resection removing as much tumor as possible since it is virtually impossible to obtain free resection margins [1]. It can include pleurectomy/decortication (complete removal of involved pleural and all gross tumor) or extrapleural pneumonectomy, including in bloc resection of pleura, lung diaphragm, and often also part of pericardium [38].

Some studies assessed a second-step surgery, following an induction chemotherapy, which is reported as a trimodality approach. Different combined modality regimens have been investigated.

The European Organization for Research and Treatment of Cancer (EORTC) analyzed trimodality therapy in a phase II trial (EORTC 08031). Patients with MM (up to stage cT3N1M0) received induction chemotherapy (cisplatin and pemetrexed × 3) followed by surgery within 21–56 days. Forty-two out of 57 (73.7%) included patients could undergo surgery. Survival figures were positive, with an overall survival of 18.4 months and 13.9 months progression-free survival. Operative mortality was 6.4% [39].

Other phase II trial with a similar design was performed in the USA and included 77 patients, achieving an overall survival of 16.8 months, with an operative mortality of 7% [40].

Although trimodal therapy seemed feasible in selected patients with promising results, it was further evaluated in a phase III trial in the UK with negative results (MARS1 study). In this trial, mortality was as high as 18.8%, with only 45% patients undergoing surgery after induction treatment, and with a lower survival for patients undergoing surgery compared to the control arm where patients received only the induction therapy (14 vs. 19 months) [41].

However, a systematic review performed afterward, including 34 studies from 26 institutions, found highly variant results, with the median survival ranging from 9.4 to 27.5 months and surgical morbidity from 22 to 82%. Probably, it may be explained by different surgical approaches, variability in terms of surgeon's prior experience, and heterogeneity of included patients, but some patients may get benefit from this treatment [42]. A multidisciplinary team with sufficient experience should provide recommendations on the suitability of patients for trimodality therapy.

6.5.2 Surgery for staging and palliation

Control pleural effusion, talc poudrage, or even decortication in a captured lung may be performed through surgery. One study compared VATS (partial) pleurectomy vs. standard talc poudrage in 196 patients. There was no benefit in terms of survival, but control of pleural effusion and quality of life were significantly better for experimental arm at 6 and 12 months [43].

7. Conclusions

This chapter shows a review of both NCCN and ESMO guidelines besides PubMed available literature. Mesothelioma is one of those tumors with less advanced in the recent years, probably due to its aggressive nature and the limited incidence, which makes clinical research more time consuming. This is considered still as a medical need due to the lack of treatment options beyond the second line. However, research is improving and some immunooncology agents have started to show a small but significant benefit in terms of survival.

Conflict of interest

The author declares no conflict of interest.

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