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Treating Malignant Pleural Mesothelioma: An update on the situation at the dawn of 2014

A review of the current scientific literature allows us to highlight the latest updates on treating Malignant Pleural Mesothelioma (MPM). The key points from the world of science were updated in December 2013 and are summarized below to show how MPM is being treated at the dawn of 2014.

Introduction

Mesothelioma, as we know, is a rare neoplasm that usually develops in the mesothelial cells lining the surface of the pleural cavity, less frequently in the peritoneal surface area, and very rarely in the tunica vaginalis or the pericardium.
This neoplasm has a very poor **prognosis** (1) and the treatments currently used in clinical practice have not yet led to a definitive cure for this disease (2,3).
Many patients with MPM have **symptoms** that develop gradually and which are often of a respiratory nature (dyspnea, cough, thoracic pain). The presence of symptoms often leads to a diagnosis of extensive intrathoracic disease.
With respect to the **diagnosis**, we should point out that physicians should always suspect MPM if they see symptoms typically associated with a history of exposure to asbestos. However, a definitive diagnosis can always be made by performing a histological examination of an adequate sample of the neoplastic tissue.
MPM is **staged** using the same system widely employed by the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC), which is known as TNM: T(Tumor), N (lymph nodes), M (metastasis) (4).
The **clinical** takes a multidiscplinary approach towards treating MPM, based on evaluating the extent of the disease, the overall condition of the patient (including cardiopulmonary function and other comorbidities) and their agreement to undergo treatment that is more or less aggressive. In fact, we must never forget to evaluate the wishes and hopes of patients to ensure that they have the best quality of life possible in accordance with their own personal parameters.
After evaluating these parameters, the patients can be subdivided into groups depending upon the recommended treatment: **surgery or chemotherapy**.
Different studies have evaluated various clinical and pathological parameters to identify patients with a good or poor prognosis. These characteristics have a prognostic value and are defined as "**prognostic factors**".
The Cancer and Leukemia Group B (CALGB) and the European Organization for Research and Treatment of Cancer (EORTC) have identified some very interesting clinical prognostic factors (5-7). The best known prognostic factor is histology; in fact, patients with sarcomatoid mesothelioma as opposed to biphasic seem to have a worse prognosis than patients with epithelial mesothelioma.
Many biomarkers are currently being studied that could be both prognostic factors and **predictive factors**, in other words they can identify which patients respond to a certain treatment as opposed to another (8,9).
Defining the **clinical benefit** is essential for **evaluating** the effectiveness of the treatment:

- Treatment response rate
- Disease control rate
- Progression free survival
- Overall survival (10,11).

There are currently two radiographic methods for measuring the response rate used for the **Computed Tomography** (CT) evaluation: the RECIST system and the modified RECIST system (12,13, 14).
Besides CT, other radiographic methods are also used, such as PET/CT (Computed Tomography with Positron

Emission Tomography).
PET can define the metabolic activity of the body by evaluating the consumption of radiolabeled glucose that is injected as a contrast just before the scan (15). However, studies have also shown that the PET responses must be evaluated by experts only because this tool cannot be considered a gold standard diagnostic examination due to the various cases of false positives and negatives (16).
The importance of this nuclear exam is aimed at evaluating the response to the disease, tumoral activity or relapse, but the standard method for confirming the diagnosis is to perform a histological analysis.
There are also very promising biomolecular methods such as measuring the serum mesothelin-related peptide (SMRP) levels (16).

Surgery

Patients who are candidates for surgery

These are patients with resectable disease that is limited to one hemithorax and who are able to withstand surgery.
In these cases, multimodal treatment approaches can be used which involve Maximal Complete Resection (MCR) together with chemotherapy and radiation therapy.

Patients who are not candidates for surgery

These are patients whose disease is such that an MCR cannot be performed, or because they are too old and suffer from insufficient cardiopulmonary function or other comorbidities.
In these cases, chemotherapy and symptomatic treatment are the best approaches and which could actually lead to a clinical benefit.

Chemotherapy

Nowadays, MPM is treated with a **combination of drugs** rather than a **single agent**. In fact, the chemotherapy regimen of **cisplatin** combined with **pemetrexed** administered together with vitamin B12 and folic acid supplements (19), is now the standard of care for patients with non-resectable disease or who cannot undergo surgery. This decision is based on a study that showed an increase in survival using this combination versus cisplatin alone.
Other platinum-based regimens have been shown to be useful but further studies are not required to determine their efficacy (19).
The combination of **Raltitrexed** on top of cisplatin improves survival versus cisplatin alone in patients with advanced MPM who have not been treated previously (27,28).
Gemcitabine together with platinum has shown response rates with acceptable toxicity levels (29-35).
Cisplatin has also been studied with other older chemotherapy agents such as **doxorubicin** or **epirubicin**, the combination of **fluoruracil**, **mitomycin** plus **etoposide**, and the combination of **methotrexate** and **vinblastine** (36-41).
The role of **maintenance chemotherapy** with pemetrexed after completing four or six cycles of therapy with a platinum-based combination is still controversial (19).
It is important to remember that these treatments are not devoid of toxicities, even though treatment with **folic acid and vitamin B12** supplements can alleviate these side effects (20-21).
If the side effects need to be reduced, **carboplatin** can be used instead of cisplatin with pemetrexed (23-25). The treatment response rates appear to be similar and so carboplatin can be a good alternative, especially for patients who are not in good overall condition and cannot tolerate the side effects from cisplatin.
Although treatment with **single agents** is considered inferior to combinations, they still have a role as second-

line therapy (10).
Agents that have been investigated and which can be used for this purpose are cisplatin (42), carboplatin (43-44), pemetrexed (45-50), methotrexate (51), edatrexate (52), raltitrexed (53), gemcitabine (54-56), anthracycline (57-59) and vinca alkaloids (56,60,61). There are still no **predictive biomarkers** for response to chemotherapy, although research is moving forward in this area. For example, the serum levels of thymidylate synthase appear to be associated with a better response to chemotherapy and a better prognosis (22).

Experimental approaches

There are many new experimental approaches that are being studied to improve the systemic treatment of MPM.
Among new agents are angiogenesis inhibitors, such as bevacizumab (62) or thalidomide (63).
Tyrosine kinase inhibitors could also be very promising, such as sorafenib (64), sunitinib (65), imatinib (65-67), vatalanib (68) and cediranib (69).
Histone deacetylase inhibitors such as vorinostat (70-71) are also new treatments. Last but not least, immunotherapy could be very useful for treating this disease either alone or in combination with chemotherapy (72-77).

Conclusions

MPM can no longer be considered a rare disease due to the increased incidence and improved diagnostic capabilities.
It should be pointed out that there are guidelines for physicians to follow because they are considered the best treatment approach since they are based on scientific evidence.
As of now, there is no treatment that can completely cure advanced stage MPM, but there is a variety of therapeutic approaches that will allow this disease to become as chronic as possible.
It is essential that we take into account the decisions and personal wishes of the patient so that we can treat their symptoms as effectively as possible and optimize their quality of life. New experimental approaches are being studied and are very promising, although they are not yet considered as a standard treatment for MPM. However, future prospects seem to be opening up at the dawn of 2014 and while research is moving forward at the laboratory bench, we hope that the products quickly become effective tools in clinical practice.

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