

Malignant peritoneal mesothelioma: a review

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Abstract: Malignant peritoneal mesothelioma (MPM) is a very rare malignancy of the peritoneum and has a poor prognosis. Of all mesotheliomas, pleural mesothelioma is more common than MPM. In comparison to pleural mesothelioma, the link with asbestos exposure is weaker (33–50% *vs.* >80%), but it is still the best-defined risk factor. MPM spreads predominantly expansive rather than infiltrative and symptoms are related to tumor spread within the abdominal cavity. Often, MPM is encountered incidentally by diagnostic imaging or by surgery. Computed tomography scan is widely accepted as a first line modality in diagnostic imaging. In diagnostic histopathology, MPM presents some challenges. Firstly, adequate clinical information is of utmost importance to consider the possibility of the diagnosis of MPM. Furthermore, a few morphological subtypes and variants exist. The most sensitive immunohistochemical markers are calretinin (100%), WT1 (94%) and CK5/6 (89%). The malignant character of immunohistochemically demonstrated mesothelial cells is not always obvious. This paradigm somewhat changed with the advent of immunohistochemical demonstration of BAP1 (BRCA-1 associated protein 1). Loss of BAP1 expression supports a diagnosis of malignancy. The gold standard in treatment remains cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC). Targetable molecular pathways in MPM are being identified. An exciting finding was the demonstration of ALK rearrangements in a small subset of patients with MPM and it is hoped for that at least this small subgroup of patients could benefit from treatment with ALK inhibitors. First-generation tyrosine kinase inhibitors against epidermal growth factor receptor (EGFR) did not show any significant activity in MPM. In contrast, nintedanib, an angiokinase inhibitor, improved progression-free survival and bevacizumab, a humanized anti-VEGF antibody increased overall survival in patients with MPM, when administered in combination with cisplatin and pemetrexed. Ongoing immunotherapy trials will offer a possible new treatment.

Keywords: Cancer treatment protocols; clinical oncology; epidemiology; malignant mesothelioma; molecular biology

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Introduction

Malignant peritoneal mesothelioma (MPM) is a very rare malignancy of the serosal membranes. It was first reported by Miller and Wynn in 1908 (1). The authors described the case of a 32-year-old male patient, presenting with abdominal pain and ascetic fluid. On examination, a diffuse

intraperitoneal neoplastic process was found, which was not amenable to surgical resection. The patient was treated symptomatically and passed away within a year (1).

Of all malignant mesotheliomas, pleural mesotheliomas are more common than MPM. It is estimated that 10–30% of all mesothelioma cases originate from the peritoneum (2). Several epidemiological differences between pleural

mesothelioma and MPM have been reported. The median age at diagnosis is earlier in MPM (63 *vs.* 71 years). Pleural mesothelioma is more frequent in males, while MPM is more frequent in females. MPM in female patients also often occurs at a younger age than MPM in male patients. The incidence of cases of MPM not related to asbestosis exposure is higher. Furthermore, the latency period between asbestos exposure and the development of mesothelioma is shorter in MPN (20 years), compared to pleural mesothelioma (30–40 years). The link with asbestos exposure is weaker than in pleural mesothelioma (33–50% *vs.* >80%), but it does not mean that asbestos exposure is negligible: it is still the best-defined risk factor (3).

Clinical findings

MPM spreads predominantly expansive more than infiltrative. Symptoms are related to the extent of tumor spread within the abdominal cavity. The most frequently reported symptoms, occurring in more than 30–50% of patients, are abdominal pain and distention, partially due to ascetic fluid. Intestinal obstruction also can occur. Other symptoms include weight loss, abdominal mass, anorexia and a new onset abdominal wall hernia (4,5). Often, mesothelioma is encountered incidentally, either on cross-sectional imaging or during abdominal laparoscopy or laparotomy. The non-specific character of the symptoms can lead to a diagnosis of MPM at a higher stage.

Diagnostic imaging

When a patient presents with abdominal pain and distention, computed tomography (CT) scan is widely accepted as a first line modality in diagnostic imaging (6). On CT scan, MPM appears as a solid, heterogeneous soft tissue mass with irregular margins, enhanced using intravenous contrast. Since MPM spreads rather expansively than infiltratively, a diffuse distribution throughout the abdominal cavity should raise suspicion of MPM. On the other hand, when no primary tumor site is found, no significantly enlarged lymph nodes are present and no organ metastases (e.g., liver) are seen, a diagnosis of MPM still must be considered. Most patients present with ascetic fluid. Other findings include caking, thickening or masses in the omentum or the mesenterium (6).

Although MRI can be used for more accurate estimation of disease burden, the usefulness for diagnostic purposes is not yet well defined (7). Also, the role of a PET or PET/

CT is unclear (8).

A scoring system for small bowel and mesenteric involvement has been developed based on assessment by contrast enhanced CT (9).

Diagnostic histopathology

MPM currently presents some challenges in histopathologic diagnosis (10). At first, adequate clinical information is of utmost importance for the pathologist to at least consider the possibility of the diagnosis of MPM. Morphologically, there are mainly three subtypes, namely epithelioid, sarcomatoid or biphasic subtype, but a bewildering number of variants exists. Pleomorphic, decidual, small, vacuolated and clear cell variants have also been described.

Since MPM tumor cells stain almost always with pan-cytokeratin markers, it is tempting for a pathologist to make a diagnosis of metastatic carcinoma. In a study of 244 cases of MPM, Tandon *et al.* found that the most sensitive immunohistochemical markers were calretinin (100%), WT1 (94%) and CK5/6 (89%) (11). D2-40 was positive in 80% of cases. Although these markers were sensitive, none of them can be considered 100% specific. As such, a panel of markers is needed. Even if the presence of numerous mesothelial cells can be demonstrated, the malignant character of these cells is not always obvious. This limits the usefulness of examining ascetic fluid. Till recently, tissue biopsies were needed to clearly demonstrate invasive growth.

This paradigm somewhat changed with the advent of the immunohistochemical demonstration of BAP1 (BRCA-1 associated protein 1), a powerful tumor suppressor. BAP1 localizes in the nucleus and cytoplasm. In the nucleus, BAP1 regulates DNA repair by homologous recombination (12). Loss of BAP1 expression supports a diagnosis of malignancy.

In the cohort of Tandon (11), 45% of cases were BAP1+, which included 42% of epithelioid tumor and 50% of biphasic tumors. BAP1 IHC is also particularly useful in deciding if mesothelial cells in cytology specimens are malignant or non-malignant (reactive). Another interesting finding is, that germline mutations in BAP1 increase susceptibility to mesothelioma, both pleural and peritoneal, uveal and cutaneous melanomas, renal cell carcinomas as well as, although less frequently, to other cancer types (13).

A recommendation was made that at least patients with mesothelioma occurring at a young age (<50 years old), in patients with multiple family members affected by mesothelioma or other cancers associated with germline

BAP1 mutations should be tested for BAP1 mutations (14).

Staging

Due to the infrequency of nodal and metastatic spreads, MPM does not fit well into a typical TNM staging system. Yan *et al.* [2011] proposed a staging system based on the extent of peritoneal disease burden (T), intra-abdominal nodal metastasis (N) and extra-abdominal metastasis (M) (15).

The T stage is determined by calculating the peritoneal carcinomatosis index (PCI). PCI codifies the extent of disease in the abdomen: a score of 0 (no gross disease) to 3 (extensive disease) is assigned to the nine quadrants of the abdominal cavity and the four segments of the small bowel and mesentery (16).

The proposed TNM staging system stratifies PCI into quartiles (1–10, 11–20, 21–30, >30) as surrogate for the T stages 1–4. Based on this system, stages were enumerated based on survival. Patients with T1N0M0 disease demonstrated a 5-year survival of 87% and are grouped as stage I. Patients with T2N0M0 or T3N0M0 demonstrated a similar 5-year survival of 53% and are designed as stage II. The five-year survival for patients with T4M0 and/or M1 disease are similarly poor (29%) and are categorized as stage III.

Treatment

Advances in surgical techniques have led to extensive investigation of cytoreductive surgery (CRS) as a modality which can potentially delay or halt aggressive local spread. Numerous publications already demonstrated the efficiency of combining CRS with chemotherapy (17).

Several chemotherapeutic delivery methods have been utilized. Hyperthermic intraperitoneal chemotherapy (HIPEC) is delivered during surgery, whereas normothermic early postoperative chemotherapy (EPIC) is delivered following completion of CRS (as early as postoperative day 1 and continuing for up to 7 days). Sequential chemotherapy (SIC) may be delivered intraperitoneally or systemically and is administered in the immediate postoperative period or anytime thereafter (18).

CRS and HIPEC have emerged as the preferential initial treatment in select patients with MPM, extending overall survival from a median of 6 months in treatment-naïve patients to 34–92 months for those undergoing CRS and HIPEC (15,17,19,20).

The choice of chemotherapy for HIPEC regimen is still matter of debate. The recently published RENAPE

study, a large study comprising 249 patients, seems to show improved overall survival when combining chemotherapeutic agents, especially with platinum-based regimens (21). The main determinant of outcome in combined CRS and HIPEC is the completeness of surgical cytoreduction. The aim of surgery is a complete macroscopic removal, by a combination of peritonectomies and visceral resections. The likelihood of achieving a complete cytoreduction depends on disease volume as well as on distribution. Disease volume can be estimated by preoperative imaging, although there are limitations for small lesions. Certain radiological criteria have been reported to predict completeness of cytoreduction. Yan *et al.* identified the presence of a >5 cm mass in the epigastric region and the loss of normal architecture of the small bowel and its mesentery, as significant predictors. Patients without these CT findings had a 94% probability of undergoing a complete cytoreduction (15,22). Unfortunately, imaging alone is often insufficient to exclude low volume or “military” small bowel disease.

Several other factors have been identified that should influence the selection of MPM patients for HIPEC, including patient performance status, age (>60 years), biphasic or sarcomatoid histology, deep tissue invasion. Also, preoperative thrombocytosis seems to be important. In an institutional analysis of 100 patients with MPM treated with CRS and HIPEC, patients with preoperative thrombocytosis had a median survival of 13 months, versus 58 months for those with normal platelet levels (23).

Residual disease after CRS can be recorded using the completeness of cytoreduction score (CCscore). CC-0 means no visible residual disease, CC-1 means residual disease <2.5 mm, and CC-2 means residual disease >2.5 mm (24).

According to the RENAPE study, overall survival was better in CC-0 (i.e., optimal CRS) patients with an epithelioid histological subtype in the “two drugs group” versus the “one-drug” group. A meta-analysis of 20 studies, that included 1,047 patients with MPM treated with CRS-HIPEC, showed a 5-year survival of 42% in the 67% of patients that achieved a complete or near complete cytoreduction prior to HIPEC (17). Without treatment, median survival has been reported from less than 5 months to up to 12 months from the time of diagnosis (25).

Systemic therapy is the alternative treatment for patients that are inoperable or wish to pursue non-surgical management. The efficacy of pemetrexed alone or in combination with cisplatin for MPM was reported in two studies, which showed that the median survival for

pemetrexed alone was 8.7 months compared to 13.1 months for patients who received cisplatin as well. The response rate was 26% and the disease control rate (stable + response) was 71.2% (26,27). Replacing cisplatin with carboplatin showed to have similar efficiency, with 24% objective response rate and 76% disease control rate. Carboplatin tends to be better tolerated than cisplatin, so this regimen has been proposed for palliative and older patients (28). The use of neoadjuvant chemotherapy is questionable. In a recent study evaluating different chemotherapy strategies, patients who received preoperative systemic chemotherapy had a similar survival. Preoperative systemic chemotherapy didn't affect the rates of complete cytoreduction (29). These results and the general lack of good responses to systemic therapy suggest that upfront CRS and HIPEC are preferable.

A recent study refined these observations (29). Naffouje *et al.* [2018] showed that the addition of chemotherapy to CRS provided a short-time survival improvement of 1 year only and was similar whether given the neoadjuvant setting. It did not add survival benefit beyond the 1-year time point.

Molecular therapy and immunotherapy

Most research, identifying relevant molecular pathways, has been performed in pleural mesothelioma. Nevertheless, targetable pathways in MPM are being identified. An exciting finding was the demonstration of ALK rearrangements in MPM (30). While pleural mesotheliomas did not show ALK rearrangement, 3% of the patients with MPM did. The ALK rearrangement was more prevalent in younger patients (>40 years) and no asbestos fibers could be detected. The typical genetic abnormalities present in MPM, such as loss of chromosomal region 9p or 22q or genetic alterations in BAP1, SETD2 or NF2 were absent. It is hoped for that at least this small subgroup of patients could benefit from treatment with ALK inhibitors.

Also, the first-generation tyrosine kinase inhibitors erlotinib and gefitinib, which target the epidermal growth factor receptor (EGFR), were shown not to display any significant activity in malignant mesothelioma cases (31).

In contrast, a recent phase II trial found that nintedanib, an angiokine inhibitor which targets vascular endothelial growth factor (VEGF) receptors, platelet-derived growth factors, fibroblastic growth factor receptors and Src and Abl kinase signaling, improved the progression-free survival for patients with MPM when administered in combination with pemetrexed and cisplatin (32). Bevacizumab, a humanized

anti-VEGF antibody, in combination with cisplatin and pemetrexed, significantly increased overall survival in a phase III trial (33).

Immune checkpoint inhibitors including anti-CTLA4 (tremelimumab and ipilimumab) and anti-PD1 antibodies (avelumab and durvalumab) are currently undergoing intensive investigations in relevant mesothelioma trials.

Conclusions

MPM is a very rare malignancy with poor prognosis. Diagnosing MPM is still challenging, also for the pathologist. Adequate clinical information is of utmost importance in making a diagnosis. A recently introduced immunohistochemical marker—BAP1—is not only helpful in making the diagnosis, but also in making a distinction between benign mesothelial hyperplasia and MPM. Testing for germline BAP1 mutations should be considered in young patients or in patients with a relevant family history. The gold standard treatment remains CRS combined with HIPEC. Recently described ALK-rearrangements in a small number of patients could often benefit with ALK inhibitor treatment. Also, nintedanib and bevacizumab should be considered in the treatment. Ongoing immunotherapy trials will offer a possible new treatment. Participation in these trials should be encouraged.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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