Editorial

Malignant pleural mesothelioma: main topics of American Society of Clinical Oncology clinical practice guidelines for diagnosis and treatment

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Malignant pleural mesothelioma (MPM) is a rare, asbestos-related neoplasm with a poor prognosis. Men are more often affected than women and the incidence in males in the US is 1.5/100,000/year (according to data in the SEER database), in Turkey it is 2.88/100,000/year and in Great Britain it is 5.4/100,000/year (1,2).

The disease is usually discovered in an advance stage, 30 or even 50 years after asbestos exposure (3). The median overall survival (OS) is about 1 year after diagnosis (3). This prognosis has not improved significantly over the past decades because the studies for the development of new therapeutic strategies are limited by the rarity of this malignancy. Recently a multidisciplinary group of experts convened by the American Society of Clinical Oncology (ASCO) presented their proposal for an approach to diagnostics and therapy of MPM (4). The authors compiled detailed guidelines based on systematic reviews, meta-analyses, randomized controlled trials and prospective and retrospective comparative observational studies that were published between 1990 and 2017 in peer-reviewed journals (4).

Diagnosis

The diagnosis of MPM should always be the result of the microscopic examination of cytological or histological samples in the context of clinical, radiological and surgical findings (5). For patients with suspected MPM who present with a pleural effusion, ASCO advocates thoracentesis as an initial intervention. A cytopathological analysis of the pleural fluid supported by immunohistochemistry (IHC) is a screening test for MPM and may help to differentiate between MPM and other cancers (3-5). Immunohistochemical tests are mandatory for a primary diagnosis of mesothelioma and a comprehensive panel of markers expected to be positive (calretinin, cytokeratins 5/6, WT-1 and podoplanin/D2-40) and negative for MPM should be performed (3-5). The choice of a negative panel depends on the differential diagnosis that is taken into consideration (5). ASCO does not define the number of required reactions, while the guidelines established by the European Society for Medical Oncology (ESMO) suggest at least two positive and two negative markers (3,4). However, none of those guidelines stresses clearly enough that cytology samples should be preserved not only as smears but also as cell blocks (cytoblocks), as these represent the best cytological material for IHC or molecular studies. Such a methodology is recommended for the diagnostic approach to cytological samples in lung carcinoma (6).

A differentiation between MPM and a benign, reactive mesothelial proliferation in cytological samples is usually impossible since many of MPMs lack the evident cytological features of malignancy (4). Immunohistochemical markers commonly used for this purpose by pathologists such as p53, desmin, EMA, GLUT-1 and IMP3 are of limited value due to their poor sensitivity and specificity (5). The International Mesothelioma Interest Group (IMIG) and ASCO guidelines recommend the use of promising new markers of MPM, i.e., loss of BAP-1 found by IHC and homozygous deletion of *p16* detected by fluorescence *in situ* hybridization (FISH) but their practical usefulness requires further investigation (4,5).

All recent guidelines agree that the most reliable method, a "gold standard", for establishing a definitive diagnosis of MPM is a histologic examination of a tissue biopsy sample, thus a histological confirmation of a cytological diagnosis is recommended in all patients in whom treatment is planned (3,4). A surgical (thoracoscopic or open) pleural biopsy is preferred but if it is contraindicated, a core needle biopsy of an accessible lesion is acceptable (3,4). Biopsies should be of a sufficient depth to enable a pathologist to recognize tissue invasion (the crucial feature of the malignant nature of the lesion) and of sufficient size for all necessary immunohistochemical tests required for a confirmation of mesothelial differentiation of a neoplasm (3,4). ASCO strongly recommends the performing a surgical biopsy in the area that would be subsequently surgically resected to avoid tumor cells being implanted into the chest wall, however prophylactic irradiation of intervention tracts is not suggested (4). A pathological report of a histologic examination should concentrate on the diagnosis of MPM but a histological subtype (epithelioid, sarcomatoid or biphasic) of a neoplasm should also be described due to its prognostic and predictive significance (3,4). A sarcomatoid subtype has the worst prognosis, often is resistant to chemotherapy, in addition surgery does not improve survival in patients with this histology (4). For biphasic tumors ASCO proposes the quantification of an epithelioid *vs.* sarcomatoid component, even in surgical pleural biopsies, because the percentage of an epithelioid component is regarded as an independent prognostic factor of an OS (4). However, if such quantification may be justified in the tumor tissue after a maximal surgical cytoreduction when multiple samples may be analyzed (7), small biopsy sample does not seem to be representative enough for this evaluation.

The usefulness of non-tissue-based biomarkers (soluble mesothelin, osteopontin or fibulin-3) as well as tumor genomic sequencing in MPM is still under evaluation. ASCO does not recommend evaluation of these markers and molecular diagnostics in routine clinical practice due to their unsatisfactory sensitivity or specificity in predicting of prognosis or monitoring of tumor response (4).

Staging

The chest and upper abdomen computed tomography (CT) with contrast enhancement is recommended as a method of choice in the initial assessment of a MPM stage. CT may be supported by magnetic resonance imaging (MRI) as it provides a better soft tissue contrast and it enables a more accurate detection of a chest wall, mediastinal, diaphragmatic and lung invasion (4,8,9). Some authors postulate that MRI with fat suppression images and cine sequences may improve an assessment of resectability of the neoplasm (10). Despite having many advantages, MRI is not commonly used due to its high cost and usually long imaging time and it is not mentioned in the ASCO guidelines as a leading imaging method for MPM (4).

FDG PET-CT (fluorodeoxyglucose, positron emission tomography-CT) scanning is recommended by ASCO as an early assessment of the staging of MPM especially for candidates for surgical treatment (4). This method of imaging can help to differentiate between a benign and malignant pleural lesion, to evaluate an intrathoracic and extrathoracic extent of the disease with better accuracy than a conventional CT and to assess the probability of metastatic disease. However, PET-CT findings should be confirmed by biopsy and a microscopic examination to avoid false negative and false positive results. A major problem is an interpretation of the PET-CT results after pleurodesis (a talc poudrage of pleural cavity). A pleural inflammation generated by this procedure increases the maximum standardized uptake value (SUVmax) and renders a false positive PET-CT result (4,11).

In patients who are considered suitable to undergo a maximal surgical cytoreduction, the radiological findings should be confirmed with additional procedures. The assessment of the extent of the disease on the pleural surfaces requires a surgical exploration by video-assisted thoracoscopic surgery (VATS) and a potential mediastinal, hilar or supraclavicular lymph node involvement should be confirmed microscopically in samples obtained by EBUS/EUS-guides fine needle aspiration, mediastinoscopy or direct needle biopsy (3,4).

Surgery

Due to the complicated anatomy of the pleural surface a complete resection of MPM is almost impossible. A maximal surgical cytoreduction is a surgical procedure whose aim is to achieve a macroscopic complete resection by removing as much visible neoplastic tissue as possible. ASCO strongly recommends that it should be offered to patients with epithelioid histology and an early stage of the disease and who are able to receive the multimodality treatment, adjuvant or neoadjuvant. Sarcomatoid histology is a contraindication to surgery, but the recommendations concerning a biphasic subtype are not so unequivocal (4). The National Comprehensive Cancer Network (NCCN) guidelines (Version 2.2108) do not recommend surgery in a biphasic subtype (12). The ESMO guidelines do not correlate indications to the surgical treatment with the histological subtype of MPM (3).

A maximal surgical cytoreduction involves extrapleural pneumonectomy (EPP; *en bloc* removal of an involved parietal and visceral pleura and the lung; the diaphragm or pericardium can also be removed), pleurectomy/decortication (P/D; removal of the involved parietal and visceral pleura) and extended P/D (EPD; P/D plus removal of the diaphragm or the pericardium). The ASCO experts recommend lung-sparing procedures, i.e., P/D or EPD, as the methods of choice (4). The authors postulate that EPP should be performed only in highly specialized centers if a lung-sparing procedure is insufficient to achieve a macroscopic complete resection. The recommendation is based on the findings in the literature that EPP and P/D (or EPD) have the similar oncological result but EPP is burdened with a higher perioperative morbidity and mortality (4). A similar opinion is presented by the NCCN guidelines, but the ESMO recommendations are not so decisive (3,4,12).

Since a maximal surgical cytoreduction is not expected to achieve a complete resection of a tumor, the current guidelines postulate that surgery alone is not sufficient for the treatment of MPM, but it is an important part of the multimodality therapy (3,4,12). Surgery should be supported by an additional antineoplastic treatment, chemotherapy and/or radiotherapy, before or after resection. Chemotherapy should be also offered to patients who are not candidates for surgery.

Chemotherapy

Both the European and American guidelines recommend pemetrexed plus platinum (usually cisplatin but carboplatin is also acceptable) with folic acid and vitamin B12 supplementation as first-line chemotherapy but ASCO strongly advises also offering the patient the option of enrolling in clinical trials that are investigating new modalities (3,4,12). A median OS of patients treated with a combination of pemetrexed/cisplatin is about 12 months. In a select group of patients with macroscopically unresectable MPM, in a good performance status, with no cardiovascular comorbidity and coagulation disorders ASCO and the NCCN propose to add bevacizumab to the pemetrexed/cisplatin regimen (3,4,12). This recommendation is based on the results of a clinical trial (Mesothelioma Avastin Cisplatin Pemetrexed Study, MAPS) that demonstrated an improvement of a progression-free and OS (about 2 months) in a group of patients who received all three agents (4). However, the FDA has not yet given its approval for the use of bevacizumab in the treatment of MPM. An interesting alternative for bevacizumab may be an agent of similar activity—nintedanib (not mentioned in the ASCO guidelines) (13). Grosso *et al.* in phase II/III LUME-Meso trial showed that a median OS in a group of patients with epithelioid histology treated with a triplet of pemetrexed/cisplatin/nintedanib was 20.6 *vs.* 15.2 months in placebo group. The trial is still ongoing thus the preliminary results need to be confirmed (13).

There are no satisfactory standards of second-line therapy for patients with a progression of MPM thus their participation in clinical trials is strongly recommended. If there is no such an option, vinorelbine or gemcitabine may be used or retreatment with pemetrexed may be considered if a good response after first-line therapy was noted (4,12). The NCCN also advises immunotherapy and suggests the administration of checkpoints inhibitors: nivolumab ± ipilimumab or pembrolizumab (12). Maio *et al.* do not mention such modality in ASCO guidelines since most of the clinical trials analyzing efficacy and safety of such a treatment are still ongoing and the final results are not available in the literature yet. The first checkpoint inhibitor assessed in relapsed MPM in randomized clinical trial (DETERMINE) was tremelimumab (CTLA-4 inhibitor) but no significant improvement in a progression free and OS in patients cured with this agent was observed (14). In the phase 1b KEYNOTE-028 trial the activity and safety of pembrolizumab was assessed in PD-L1-positive MPM. Preliminary results revealed that a median OS was among the longest for the second-line therapy (5.7–10.9 months) (15). In other clinical trials nivolumab in monotherapy *vs.* a

combination with ipilimumab in second and third-line of therapy is tested (a phase II MAPS2 trial) and a doublet of nivolumab/ipilimumab is compared with pemetrexed/cisplatin as first-line regimen in unresectable MPM (a phase III CheckMated743 trial, NCT02899299) (16). Immunotherapy may be a chance for patients with sarcomatoid MPM that features the worst prognosis, which is usually resistant to chemotherapy and disqualifies a patient from surgery. An expression of PD-L1 on neoplastic cells regarded as predictive biomarker that predisposes to a good response to immunotherapy was noted in these tumors (17,18).

Radiotherapy

Radiation therapy (RT) may be offered to select patients with MPM as a part of the multimodality treatment but all the current guidelines emphasize that due to intensive toxicity of RT it should be performed in highly specialized centers by experienced radiation oncologists (3,4,12). ASCO supports an option of adjuvant RT in patients who underwent EPP and are in a good performance status because delayed locoregional recurrence after irradiation was observed (4). 3D conformal radiation therapy (CRT) or intensity-modulated RT (IMRT) are preferred techniques due to their high level of precision in dose distribution (3,4,12). Neoadjuvant RT before EPP or adjuvant IMRT after lung-sparing surgery (P/D, EPD) may be considered especially in the context of clinical trials but neoadjuvant RT before P/D (EPD) is strongly discounseled due to the high risk of severe post-radiation pneumonitis (4,12).

Monitoring of response to therapy

An assessment of MPM response to therapy requires tumor measurement according to modified Response Evaluation Criteria in Solid Tumors (RECIST) in chest CT (4). This approach is recommended and widely described by Kindler *et al.* in the ASCO guidelines but not mentioned in the previous (2015) standards of ESMO (3). A pleural thickening should be measured perpendicularly to the chest wall or mediastinum in two sites at three different levels with at least a 1 cm interval of used transverse slices. A soft tissue window and 2.5 mm slice thickness are preferred (19). The sum of all six measurements should be stored electronically and compared with corresponding tumor dimensions at follow-up CT scans (4,19). Volumetric CT-based measurements and SUVmax measurements in PET-CT imaging are not validated for assessment of tumor response to treatment and require further investigations (4).

Palliative treatment

A palliative treatment advised to patients with symptomatic pleural effusion include such surgical procedures like tunneled permanent catheter placement, VATS pleurodesis or partial pleurectomy (3,4,12). Radiotherapy is an effective and strongly recommended modality for relief of chest pain or other symptoms. In palliation any RT technique may be used since long-term adverse effects are of low significance in terminally ill patients (4).

The current ASCO guidelines are a detailed and a very useful compendium for oncologist, surgeons, radiologists and pathologists involved in diagnosis and treatment of MPM. They comprise of the results of numerous studies and answer a lot of important questions. It is emphasized that the treatment of MPM requires a multimodal approach since none of the methods alone is effective enough. Experienced specialists in centers of excellence should control each phase of the diagnostics and therapy of this rare malignancy with a poor prognosis. A spectacular breakthrough in diagnostics and treatment of MPM has not yet been made and novel and more effective methods of therapy are still demanded. Therefore, patients should be offered the option of enrolling in clinical trials.

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