BIBLIOGRAPHIC REVIEW

July 2016

Third Consensus Conference on Malignant Pleural Mesothelioma: State-of-the-art and recommendations

Introduction

Here we are once again to discuss scientific information and to disclose news about Malignant Pleural Mesothelioma (MPM).

At this time, we deem it useful to involve the readers in a new consensus conference, in other words in a meeting of experts which resulted in the drafting an update of the state-of-the-art of this topic and in the collection of recommendations on how to deal with this disease.

We are talking about the Third Italian Consensus Conference that took place in Bari back in January 2015, with the support of AIOM (Italian Association of Medical Oncology)

The resulting publication, the tangible output of the work carried out by experts on MPM, is available online at the following link:

http://www.ncbi.nlm.nih.gov/pubmed/?term=Mezzapelle+et+al%2C+Sci+Rep+6%3A+22850.

This article is organised into nine different chapters: Introduction, Methods, Epidemiology, Diagnosis, Radiological Check-ups, Surgery, Radiotherapy, Chemotherapy, Psycho-social and legal aspects and future prospects.

This review contains a collection of the main references and an outline summary of the main concepts of this Consensus Conference. For more in-depth information and more specific details, please refer to the full text.

State-of-the-art and recommendations for Malignant Pleural Mesothelioma, according to Italian experts

Epidemiological data

In 2011, the incidence of MPM in Italy was 3.49 and 1.25 cases every 100,000 people/year, respectively, for men and women. A total of 1428 cases were reported: 1035 men and 393 women (Anon, 2015). The national incidence and mortality are currently stable, and there seems to be a one-plateau trend. However, it is believed that a peak will take place in 2020-2025, especially in industrialised countries.

As everyone knows, exposure to asbestos is strictly related to the incidence of MPM, and there is a veritable dose-response relationship (Prince, 2005; Mastrangelo, 2014).

Cumulative exposure to asbestos is an indicator that takes into account the sum of the exposure and is used in various research fields. However, it fails to consider important data such as the duration or intensity of the exposure itself (Thomas, 2013; Lubin, 2006; Vlandereen, 2013; Richardson, 2012).

Nevertheless, we can safely say that, with regards to cumulative exposure to asbestos, there does not seem to be a large difference compared to the previously published Consensus Conferences (Pinto, 2011; Pinto, 2013).

Exposure to asbestos can be of the occupational type, in other words tied to the work which the patient carries out or has carried out in the past, or non-occupational, tied above all to atmospheric and domestic pollution. In Italy, it is estimated that non-occupational exposure takes place in about 10.2% of the cases (National Mesothelioma Register 2012).

Asbestos can also spread through the air under the form of fibres. The WHO (World Health Organisation) has estimated that continuous exposure to 0.4-1 fibre/l can lead to the risk of becoming ill with MPM in 0.4-0.5 cases out of 100,000 people (World Health Organisation Regional Office for Europe, 2000).

Moreover, asbestos can also be found in water; however, there is no evidence of cases of mesothelioma caused by the ingestion of fibres.

There are documented cases of asbestos-containing talc, although this has never happened on Italian soil (Finkelstein, 2012).

Other carcinogenic substances tied to asbestos that have been the cause of MPM in Italy are fluoro-edenite, as in the area of Biancavilla (CT). These cases are similar to those described in Japan, in volcanic areas.

Although there is data of cancerogenesis only in test animals and no cases of MPM were ever described in man, silica carbide is also a carcinogenic agent that can potential cause

this disease (Grosse, 2014).
There are also hereditary cases of MPM, associated with genetic alterations such as, for example, the mutations of BAP1 (Klerk, 2013; Betti, 2015. Some of these have also been described in Italy (Ascoli, 2007; Ascoli, 2014).

Diagnosis

Oftentimes, MPM manifests itself with a pleural effusion; however, this collection of fluid in the pleural cavity can also be a secondary effect of different medical conditions. Therefore, it is important to first of all proceed with a differential diagnosis between primitive tumour of the pleura, MPM, and other neoplasias that may metastasize at the pleural level, the most common ones being lung, breast and kidney neoplasias (Smith, 2014). Moreover, it is important to remember that many non-neoplastic pathologies are included within the differential diagnosis which may however cause pleural effusion: for example, infectious or inflammatory pleurisies, cardiac failure, parapneumonic effusion.
The diagnosis of MPM is carried out above all through the analysis of a pleural biopsy, which is often obtained by means of a thoracoscopy or, more rarely, by means of an eco or TC guided percutaneous biopsy (Pinto, 2013; Scherpereel, 2010; van Zandwijk, 2013).
In addition to the histological analysis carried out on the tissue obtained through a biopsy, it is also possibly to conduct a cytological analysis, evaluating the cells found in the pleural fluid. In some cases, this may allow the diagnosis to be made; however, this is exam is not as sensitive as histology (Kawai, 2014; Paintal, 2013; Hjerpe, 2015, Henderson, 2013).
In accordance with WHO, a histological classification of MPM has been defined, according to which tMPM can be subdivided into the epithelioid, sarcomatoid and biphasic histotype (Larsen, 2013).
Different markers are used to better define these tumour characteristics and, in particular to differentiate pleural metastasis from adenocarcinoma and primitive lesions caused by MPM (Ordonez, 2013; Betta, 2012).
The following markers are more commonly used to differentiate epithelioid MPM from adenocarcinomas: calretinin, D2-40 (anti-podoplanin antibody), the protein of Wilms-1 tumour, cytokeratin 5 and 6, mesothelin and thrombomodulin. Markers which are considered negative are; CEA, BerEP4, MOC-31, claudin-4 and CD155 (Henderson, 2013b; Lonardi, 2011, Jo, 2014). Napsin A, TTF1, CDX2, PAX-8, apocrine markers and hormonal receptors are instead useful for differentiating MPM from other localised metastasis at the pleural level. The marker BAP1 has been recently tested to differentiate benign mesothelial lesions from malignant ones (Cigognetti, 2015).

Sarcomatoid MPM expresses above all markers such as pan-cytokeratin, vimentin, smooth muscle differentiation markers, D2-40, calretinin (Pinto, 2013; Ordonez, 2013; Scherpereel, 2010; Churg, 2015; Henderson, 2013b).
Other useful markers for the diagnosis of MPM are mesothelin-related peptides (SMRP), osteopontin, and fibulin-3 (Lao, 2014; Creaney, 2011; Hollevoet 2011; Hollevoet, 2010; Luo, 2010; Wheatley-Price, 2010; Creaney 2014a; Franceschini, 2014).

Radiological tests

There are different radiological methods mainly used to diagnose MPM (Hallifax, 2015).
The first approach usually takes place through a chest X-ray, which normally allows to identify the presence of a pleural or pericardial effusion or even very extended pleural lesions.
The chest TC, on the other hand, is considered a second-choice exam that allows one to obtain much more detailed morphological information compared to the chest X-ray.
The ultrasound scan can be useful to visualise some specific pleural anomalies, in addition to being used as a guide for conducting a thoracentecis procedure and, if necessary, as a guide for pleural biopsies.
The PET scan can be applied above all to evaluate the metabolism of some lesions; no changes have occurred since the previous Consensus Conference (Pinto, 2013).
As regards invasive diagnostic procedures, there are no changes in indications and recommendations compared to the ones described in the previous experts' review (Pinto, 2013).
Thoracentesis is still the first minimally invasive diagnostic approach, and cytological analysis can be useful to diagnose the presence of malignant cells in about 60% of the cases. The thoracentesis procedure applied under ultrasound guidance can be useful to minimise any complications that may arise (Hooper, 2010).
Ultrasound and CT-guided biopsy have permanently replaced biopsies done blindly, and they are useful for performing accurate biopsies of lesions, irregularities or pleural thickening (Maskell, 2003; Qureshi, 2006; Adamset, 2001; Metintas, 2010a).
Thoracoscopy is the "gold standard" invasive diagnostic technique, and allows to obtain a diagnosis in 90% of the cases (Churg, 2014; Boutin, 1993; Hansen, 1998; Galbis, 2011; Brimset, 2012).
The Endo-Bronchial UltraSound (EBUS) technique, used to analyses lymph nodes that drain neoplastic cells deriving from MPM, can offer certain advantages with respect to the mediastinoscopy (Rice, 2009; Tournoy, 2008; Zielinski, 2010; Richards, 2010).

All of the radiological techniques used for diagnostic purposes also play a crucial role in establishing the stage the disease is in, thus allowing, in addition to the determination of the prognosis, a definition of the therapeutic approaches, which obviously change depending on the stage of the disease.
The methods mostly used for this purpose are still the CT scan and the PET scan (Truong, 2013a; Nickellet, 2014; Basu, 2011; Erasmus, 2005; Rice, 2009; Flores, 2003; Sørensen, 2008; Truong, 2013b; Armato, 2013; Frauenfelder, 2011; Labby, 2013a; Labby, 2013b; Byrne, 2004).

Therapeutic approaches

Surgery

Surgery plays a role in the diagnostic approach since, through invasive methods, including the ones described above, it can be extremely useful for obtaining histological material (Greillier, 2007; Buenoet, 2004; Attanoos, 2008).
Surgery is also employed in the treatment of malignant pleural effusion. In fact, in addition to being used for diagnostic purposes, thoracoscopy can also be for medical purposes since it allows the intrapleural administration of talc for the purpose of obtaining a pleurodesis. In the same way, specific surgical drainage methods can be applied for each clinical case (Waller, 1995; Halstead 2005; Martin-Ucar, 2001; Nakas, 2008).
Of course, the role of surgery in the treatment of MPM aims at the complete resection of the disease. It is important to remember that this is possible only in those cases where the MPM is resectable and, consequently, it can only be used in the earlier stages (Rice, 2011 Aug; Gomez, 2014; Treasure, 2014; Flores Pass, 2008; Lang-Lazdunski, 2012; Taioli, 2015; (Cao, 2014; Sugarbaker, 2014; Nakas, 2012).
(For specific recommendations and detailed indications of surgery in MPM, please refer to the full text of the Consensus Conference.)

Radiotherapy

In the past, radiotherapy was used to treat the progress of the section used for access of thoracoscopy or pleural drainages. In fact, it was believed that irradiating this tract would decrease the possibility of developing metastasis along the anatomical course of the optic instrument or of the drainage used during invasive procedures. However, studies are contradictory and, as of today, there is no evidence such as to suggest stopping the use of radiotherapy (Boutin, 1995; Bydder, 2004; O'Rourke, 2007).
There is no random data in support of the usefulness of adjuvant therapy for MPM.

Nevertheless, it is believed that a total dosage of 54 Gy may be associated to a reduced failure of the local treatment (Rusch, 2001). Different studies have compared radiotherapy technique with modulated intensity with standard radiotherapy. However, effective radiotherapy would seem to be the one applied to the entire hemi-thorax concerned by the disease (Forster, 2003; Rice, 2007; Stahel, 2014). At present, there is some preliminary data available on the potential use of radiotherapy with modulated intensity, used to spare the lung contained in the hemi-thorax affected by MPM (Rosenzweig, 2012; Minatel, 2014; Chance, 2015).

Palliative radiotherapy is certainly crucial for controlling the symptoms and, in particular, for pain management (Bissett, 1991; Lindén, 1996; MacLeod, 2015).

(For specific recommendations and detailed indications of radiotherapy in MPM, please refer to the full text of the Consensus Conference.)

Chemotherapy

Standard chemotherapy indications were widely described in the previous Consensus Conference (Pinto, 2013).

Nevertheless, please remember that the first therapeutic line of this disease is based on the administration of a combination of platinum salts and third-generation antifolates (Fennell, 2008; Muers, 2008; Vogelzang, 2003; Van Meerbeeck, 2005; Santoro, 2008; van den Bogaert, 2006; Buikhuisen, 2013, Anon, 2016; Ceresoli, 2008; Ceresoli 2014).

New knowledge aimed at understanding the pathogenic ways of this disease have allowed the identification of new therapeutic targets, including of the biological type (Kindler, 2012; Zalcman, 2010, Zalcman, 2015; Hassan, 2014).

The second-line therapy has not allowed a clear improvement in terms of survival compared to the support therapy only, although certain standard drugs, such as Pemetrexed, have contributed favourable data in terms of better objective response and control of the disease rate (Jassem, 2008; Ceresoli, 2014). There are no pharmaceutical agents approved for second-line therapy, consequently the possibility to enrol patients in clinical studies may be considered a good treatment opportunity.

There is still no confirmed scientific evidence concerning the use of second-line biological drugs (Ceresoli, 2014; Krug, 2015; Calabrò, 2013; Anon, 2016; Alley, 2015; Ceresoli, 2011; Bearz, 2012; Zucali, 2012).

Conclusions

Unfortunately, the efficacy of current therapies for MPM is still quite limited, and the

prognosis of this disease remains regrettably negative.

New therapeutic approaches are needed, and the research conducted in this area is offering interesting results that require confirming, randomised, multicentric and reproducible studies.

In the meantime, it is useful to continue with a strict surveillance of the subjects at risks and, consequently, there is some advice that can be easily applied.

In fact, the surveillance programmes being implemented are aimed at different objectives, such as:

- informing subjects exposed to asbestos of the possible risks associated with it, both in terms of present exposure and past exposure;
- informing the relatives of subjects exposed to asbestos and the possible risk for these individuals, even though they may have not been directly exposed;
- carefully reconstructing the patient's work history, especially entering into details of exposure to carcinogenic substances, its duration and intensity;
- arranging for spreading information concerning diagnostic and therapeutic instruments and the medical prospects available abroad as well;
- providing support for claims in order to obtain payments and compensations;
- conduct proper counselling aimed at getting people to stop smoking cigarettes and follow a proper and healthy lifestyle.

Future therapeutic prospects are just around the corner, and a series of research projects underway offer new hope for the treatment of this pathology.

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