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Chapter

Predictive and Prognosis Factors of Clinical Utility in Mesothelioma

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Abstract

The constant research in therapeutics for mesothelioma has been improving their tumor response and overall survival, generating the need to propose markers that guide the doctor's therapeutic approach in a more precise way. Recently, different predictive factors have been proposed, such as mesothelin-related peptides, fibulin-3, and osteopontin associated with an image giving information about the probability of tumor response to a therapeutic agent or a combination of agents. As is well known, the importance of prognostic markers of utility lies in providing prospective information on the evolution of the patient and thus their ability to guide therapeutic decisions. Although the clinical stage and histology are currently the most described prognostic factors, recent studies have shown interest in the expression of estrogen receptor beta and calretinin, among other promising factors. Given the heterogeneity of this broad field of research in mesothelioma, it is necessary to objectively present the prognostic and predictive factors of greater clinical utility.

Keywords: prognosis factors, predictive factors, response to treatment, clinical factors, histopathology factors, biological factors, clinical scores

1. Introduction

The prognosis of patients with mesothelioma is unfavorable, with a median survival of approximately 12 months from diagnosis [1–5]; this makes a clear need to improve the effectiveness of multimodality approaches and to define in a better way the subgroups' prognosis [6–9]. One way to achieve this objective is the use of prognostic and predictive factors; a prognostic factor provides prospective information on the evolution of the patient being able to guide therapeutic decisions, while a predictive factor gives us information on the probability of tumor response to a therapeutic agent.

The characteristics that a prognostic factor must meet are: (a) simple prediction method, (b) wide availability, (c) sensitivity, and (d) reproducibility in any clinical situation. The purpose of these markers is to help define the individual prognosis of clinical groups, select patients who may need other treatments, and assign the most effective treatments to improve survival and quality of life.

Although currently the therapeutic decisions are still based on the classic clinical and pathological prognostic factors already known, such as age, functional status, sex, chest pain, weight loss, thrombocytosis, leukocytosis, anemia, and histological type [3, 10], biological and genetic factors may soon be excellent options as prognostic and predictive factors.

2. Clinical factors

Multiple mesothelioma series have validated advanced TNM stage, age ≥ 50 years, male gender, poor performance status, weight loss, platelet counts ≥400,000, white blood cell counts ≥15.5, low hemoglobin level, low albumin levels, and high serum lactate dehydrogenase levels, among others, as poor predictive and prognosis factors [11–21].

TNM stage is one of the most studied prognosis factors describing a poor survival prognosis for those with advanced or metastatic stage, however, in the same stage of the disease, patients' survival varies widely suggesting that TNM staging is not completely precise to predict a survival outcome [16]. Moreover, with the new changes applied since the release of the eighth edition of the TNM Classification for Lung and Pleural Tumors where all patients N0M0 malignant pleural mesothelioma as stage IA or IB, differing from the seventh edition classification, in which N0 also was listed within the classifications for stages II and III. These changes reclassified as stage I many patients who were formerly considered as stage II or III since some patients at stage IB experienced poorer prognosis than those at stage III [22, 23]. Identifying prognostic factors based on the new classification should help to identify the patients with a poor prognosis who may benefit from multimodality treatments. Additional to the TNM staging system, the true tumor volume was independently associated with overall survival and response to treatment; however, more studies need to be done to validate this variable [24–27].

Previous studies have suggested that females with mesothelioma experience longer survival compared to males [6, 28–33] with possible suggested explications like those they present at earlier stage [34], tumors with more favorable histology [30], different asbestos exposure responsible for a more indolent tumor biology [35], and a protective effect of circulating estrogen interacting with estrogen receptors present in their tumors, [32, 36, 37] however, only more indolent tumor biology associated to higher frequency of germline mutations in DNA repair genes [38–41] and interaction of estrogens with estrogen receptor beta [36, 37, 42, 43], other theories still controversial [15].

Platelet count is a practical and easy blood test in clinical practice that has been studied for its role as a prognosis factor due to the interaction of platelets with tumor cells contributing to tumor progression, invasion, metastasis, and angiogenesis.[44]. This interaction could be explained by five possible pathways: the first one refers to the release of growth factor by the platelets, including transforming growth factor β and fibroblast growth factor enhancing cancer cell proliferation [45]. Second, platelet membranes are rich in many adhesin molecules like selectins, integrins, immunoglobulin superfamily proteins, and leucine-rich glycoproteins stabilizing the cancer cell arrest in the vasculature, increasing potential of metastasis [46]. Third, platelets could mediate the invasive potential of cancer cells by the release of thromboxane A2, 12-hydroxyeicosatetranoic acid, and matrix metalloproteinases [47–49]. Fourth, platelets release a large number of pro-angiogenic mediators such as vascular endothelial growth factor and basic fibroblast growth factor influencing the tumor angiogenesis and consequently tumor growth [50–52]. Fifth, some studies have demonstrated that platelets facilitate the immune escape of cancer cells by surrounding tumor cells and protecting them from the cytotoxic effect of natural killer cells [53, 54]. Several studies concluded that thrombocytosis is correlated with worse overall survival in patients with mesothelioma, indicating that pretreatment could be an adequate and useful factor of prognosis [18].

Recently, many people have focused on the role of inflammation in cancer due to its contribution to tumor initiation and malignant progression. More specifically in mesothelioma, inflammation becomes relevant since most patients have a history of asbestos exposure, and this mineral can skewer cells and set off chemical reactions

that lead to inflammation, DNA damage, and cell death [20]. Leukocyte blood count reflects a degree of the systemic inflammatory response in tumor patients, being a valuable and simple indicator [55]. Blood neutrophil-to-lymphocyte ratio is a systemic marker for inflammation closely related to the mortality rate and response to the treatment is useful as a predictive and prognostic factor, taking 3 as a dividing point [20, 56–60]. In the same way, serum c-protein can reflect an inflammatory environment; although its usefulness as a prognostic and predictive factor has been demonstrated in limited studies, more research is needed to validate its utility [61–63].

Malnutrition has been related to adverse outcomes in overall survival, quality of life, and increased mortality of malignant tumors [64–66]. Serum albumin level is a simple and objective indicator to evaluate malnutrition. Multiple studies have demonstrated hypoalbuminemia as an adverse independent prognostic factor for mesothelioma [19, 20, 67].

It is well known that cancer cells tend to employ alternate metabolic pathways, generating adenosine triphosphate through anaerobic glycolysis regulated by lactate dehydrogenase [68, 69]. Several studies assessed the value of high pretreatment lactate dehydrogenase levels for the prediction of a worse survival outcome in mesothelioma [10, 61, 62, 70–75]. The association between high lactate dehydrogenase levels and poor prognosis on malignancies has tried to be explained in multiple ways. The first theory implies that the production of lactate acid could be up-regulated by lactate dehydrogenase, generating an acidic environment activating metalloproteases, macrophage-mediated angiogenesis and protecting mitochondria from oxidative stress, which induces resistance to hypoxia-induced apoptosis of tumor cells [76–80]. The second theory explains a strong correlation between elevated lactate dehydrogenase levels and an up-regulation of the hypoxia-inducible factor pathway resulting in a host immunological function attenuation, and enhanced tumor angiogenesis, which has an adverse impact on prognosis in malignant tumors [81]. Despite the great evidence of the utility of lactate dehydrogenase as a convenient and cost-effective indicator for predicting overall survival outcome, cut-off values of lactate dehydrogenase reported on the literature are inconsistent, and it is important to standardize the cut-off value in future studies.

3. Histopathology factors

Together with the TNM stage, the histological type is one of the strongest prognostic factors among patients with mesothelioma. However, with the support of immunohistochemistry markers, not only has diagnosis been improved, but also new markers have appeared for a more accurate prediction of response to treatment, overall survival, and developing better therapeutic approaches.

The most significant prognostic factor until now remains histology with a better prognosis for epithelioid type than sarcomatoid or biphasic type mesothelioma [10, 12, 82, 83]. In addition to histologic subtyping (with solid growth pattern being associated with a poor outcome), nuclear atypia, mitotic count, and the presence of necrosis were found to be independent prognostic factors in epithelioid malignant pleural mesothelioma [84–86].

Ki67 antigen is used for the assessment of growth fraction of cell populations, due to it being exclusively expressed in proliferating cells; cell cycle analysis showed that Ki67 is detectable in G1, G2, S, and mitosis phases but absent in quiescent cells [87, 88]. Despite most studies indicating that high expression of Ki67 leads to a poor prognosis, some malignancies showing high Ki67 levels actually show a better response to treatment, which could be explained by the fact that cells with high proliferation are susceptible to cytotoxic agents [89–93]. The detection of Ki67 is not a routine procedure for mesothelioma's diagnosis and treatment; however, a

group has suggested to consider it due to its utility as a possible prognostic marker in epithelioid mesothelioma with a better prognosis outcome in those with low expression levels [94–98].

Calretinin is a calcium-binding protein that has been established as a useful marker in distinguishing mesothelioma from adenocarcinomas with pleural metastases [99]; Additionally, interest in using higher calretinin scores as favorable prognostic factors has been growing, although further investigation is needed [100–104].

As mentioned above in the section of clinical factors, estrogen receptor beta expressed on mesothelial tumor cells has become a promising prognostic factor and a possible future therapeutic target [36, 37, 42, 43].

4. Biological factors

Several biomarkers are selectively elevated in patients with mesothelioma. However, further study and validation are required before they are recommended as routine predictive or prognosis factors and they should be adjunct to a radiological assessment. With considerable variation in response to treatment, the emergence of promising biomarkers that could select responders from non-responders at baseline or during treatment would guide to a better therapeutic approach, prevent patients from getting ineffective treatments, and improve cost-effectiveness.

The most researched biomarker until now is the mesothelin; soluble mesothelin is a circulating form of a membrane-bound glycoprotein highly expressed by mesothelial cells in mesothelioma (predominantly epithelioid type) and other malignancies [105]. Despite the controversial evidence reported in the literature [106–114], a meta-analysis conducted by Tian et al. [115] concluded that a high soluble mesothelin level may lead to a poor prognosis for patients with mesothelioma, it being appropriate to consider mesothelin level as an independent prognostic marker.

Human fibulin-3 is a secreted glycoprotein that plays an essential role in the regulation of cell proliferation and migration [116, 117]. Recent findings have documented altered levels on patients with mesothelioma, highlighting them as a novel biomarker for this malignancy; however, as most studies have been done with limited sample size [114, 118–120], and the results may not completely mirror the actual value of fibulin-3 for prognosis, further studies are needed for a more comprehensive prognostic role of human fibulin-3 in mesothelioma.

Osteopontin is a glycoprotein that mediates cell-matrix interactions with adverse outcomes for mesothelioma [98, 121, 122]; however, its utility is limited because of the significant variability in the cut-offs used between studies. In order to be validated in the future, a consensus approach is required for sampling and analysis [122].

CA 125 is a transmembrane glycoprotein that can be detected in the fallopian tube, endometrium, endocervix, and mesothelial surface of the peritoneum, pleura, and pericardium [98]. Some cases with non-gynecological cancer showed positive immunohistochemical staining for CA125 in tumor tissue and elevated CA 125 levels in serum [123–125]. The baseline levels of serum CA125 accompanied by the stage of the disease could be used as independent prognostic factors for patients with mesothelioma; the change in serum CA125 levels can predict overall survival and response to systemic treatments [126–128].

5. Clinical scores

The best-known clinical prognostic scoring systems for mesothelioma until now derive from the Cancer and Leukemia Group B (CALGB) and the European

Organization for Research and Treatment of Cancer (EORTC), both scores have been widely used to better select patients who have a favorable prognosis and could tolerate and potentially benefit from a more aggressive combined modality treatment [3, 10].

The CALGB index was validated by examining the survival of a wide cohort dividing patients into six patient subgroups with different survival rates. The CALGB study considered extent pleural disease, lactate dehydrogenase >500 UI/L, poor performance status, platelets >400,000, non-epithelial histology, and >75 years as negative prognostic factors for survival. The most favorable characteristics were a performance status of 0, age < 49, and hemoglobin ≥14.6/μl [10].

The EORTC score has been validated in 523 patients included in 10 mesothelioma trials with the analysis suggesting that performance status >0, stage IV disease, and biphasic or sarcomatous histologies are associated with a worse outcome [129]. Additional reports confirmed that male sex, older age, and abnormal hematological values also give a poor prognosis [13, 130].

Despite both studies identifying performance status and histology as two main prognostic factors, these analyses included patients with heterogeneous tumor stages at diagnosis, the majority of whom underwent major surgery and whose treatment predated the use of pemetrexed as first-line treatment. Since the positioning of pemetrexed as a first-line treatment, no validated prognostic score has appeared, resulting in the need to generate new studies with the aforementioned scores [131].

6. Promising factors

Although there are multiple prognostic and predictive factors that are currently validated, many others have generated great interest for their potential as a therapeutic target in the future.

There is an increasing interest in the use of semi-quantitative ^{18}F-FDG PET/CT parameters, like metabolic tumor volume and total lesion glycolysis to measure the metabolic activity in the entire tumor volume with great potential to predict response to treatment [119, 132–144]; however further investigation is needed in mesothelioma patients.

Despite the wide utility of the tissue biopsy, the invasive nature limits their application, especially when repeated biopsies are needed. Given the aforementioned, liquid biopsy has gained interest from oncologists and basic researchers [145]. Although liquid biopsy is still far from replacing tissue biopsy for mesothelioma, plasma and serum samples represent minimally invasive, low-risk, and easily obtained biological fluids that many studies have indicated as potentially interesting prognosis biomarkers as mentioned in the section "Biological factors" [146].

Nowadays, immunotherapy is gaining great relevance in cancer therapeutics. Soon, oncologists will routinely ask for programmed death-ligand 1 (PD-L1) status that has been correlated with better treatment response to anti-PD-L1 antibodies and overall survival outcomes [147–151]. However, different PD-L1 antibodies coupled with specific staining platforms and scoring criteria may be necessary since finding a suitable cut-off point remains a current challenge [151, 152].

A wide number of molecular prognostic markers for mesothelioma have been investigated. The number of tumor-infiltrating myeloid cells, c-MET expression, thymidylate synthase expression, among others, represent promising biomarkers associated with strong prognostic significance. c-MET is a tyrosine kinase receptor, its overexpression was associated with longer overall survival in patients with mesothelioma [98, 153]. Thymidylate synthase expression may predict pemetrexed

efficacy, a certain correlation has also been found with overall survival and progression-free survival [154].

Dysregulated genes play a critical role in the development and progression of mesothelioma, making them future diagnosis and prognosis biomarkers [155]. Recently, Zhou et al. obtained an RNA-Seq count quantified by RSEM for RNA expression profiles of a large cohort of patients with mesothelioma according to The Cancer Genome Atlas guidelines. After a time-dependent receiver operated a characteristic curve to evaluate the prognostic performance of survival prediction, three genes (LSM6, GZMB, and HJURP) were found with a strong statistically significant prognostic association; this prognostic signature could be a clinically useful tool that in the future could be incorporated into a clinical sequencing program to individualize therapy [156].

7. Conclusion

Despite the wide variety of predictive and prognostic factors that exist, just a few are replicable worldwide. Furthermore, only pathological type and performance status are the grade-A recommendations of prognostic factors in pretreatment assessment, as well as the nodal stage, residual disease, and histology during treatment [16].

Although there is currently no validated prognostic approach, according to individual evidence, availability, and cost-benefit, it is recommended to pay special attention to the TNM classification, histological type, and serum CA125 in the decision for multimodal therapy. Despite the practicality of the prognostic scoring systems, further investigations are needed to validate the known scores or generated new ones that fit the new existing therapeutic modalities for mesothelioma.

In the near future, many other prognostic and predictive factors may be introduced in clinical practice making a selection of mesothelioma subgroups to improve the benefit achievable by currently available treatment strategies, and relentless efforts will have to be focused on designing innovative compounds selectively targeting the existing (or additional) markers to improve the grim prognosis of the disease.

Conflict of interest

Dr. Jeronimo Rafael Rodríguez-Cid has educational, investigational and advice relations with MSD, Bristol Myers, Roche, Takeda, Amgen, Abvie, Aztra Zeneca, Boehringer Ingelheim, Pfizer, Celgen, Novartis, and Bayer.

Dr. Rodrigo Rafael Flores-Mariñelarena have no conflicts of interest to declare.

Notes/Thanks/Other declarations

None to declare.

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