Editorial

Malignant pleural effusion: first steps towards therapy

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Malignant pleural effusion (MPE): first steps towards therapy

MPE consists in the accumulation of fluid in the pleural space due to a malignant disease. MPE is a difficult to treat clinical condition which frequently results in severe symptoms like dyspnoea (that can be invalidating) or pain, and poor quality of live. The majority of MPE is caused by metastases from distant cancers, most commonly from the lungs and breast (1), but it is possible to occur in almost all types of cancer, and up to 15% of all patients with any malignant disease have an MPE (2). This condition affects 500–700 individuals per million population annually (3).

Despite the progress in cancer treatment in recent years, at present, there are not curative options for this complication, and the management of MPE is basically palliative, with a median survival of patients ranging from 3 to 12 months (1,2). Those patients expected to survive more than 3 months would need interventional procedures (chemical pleurodesis or indwelling pleural catheters) performed for improving symptoms and quality of life. Those patients with shorter life expectancy (less than 3 months) benefits of palliative, non-invasive, care (2,3). However, it is difficult to elucidate in clinical practice which patients will actually survive long enough to be eligible for pleural interventions. To this end, several clinical and biochemical indices have been proposed (2). Among biochemical parameters evaluated to predict survival and aid in decision-making, pleural fluid pH level has been widely used. However, a meta-analysis concluded that, although pH below 7.28 was indicative, in general, of shorter survival, the pH value was not capable to predict 3-month survival (4). Numerous other unvalidated prognostic indices have been described (2), mainly for primary pleural tumours, but these tests are not yet reliable for clinical use.

Patient prognosis is highly variable and depends on different factors. After evaluating different combinations of data from patients with MPE, Clive *et al.* (5) proposed a scale, denominated LENT prognostic score, as a tool able to predict survival with clinical decision purposes. LENT score includes the level of lactate dehydrogenase measured in pleural fluid, the performance score from the Eastern Cooperative Oncology Group (ECOG) scale (index that assess how the disease affects the daily living activities of a patient), the ratio between neutrophils and lymphocytes and the type of tumour affecting the patient.

Very recently, Psallidas *et al.* (6) proposed a new prognostic score for patients with MPE that performs better than LENT score. This new score, denominated PROMISE, includes clinical and laboratory data and can be used with measures available from standard clinical practice (the so-called clinical PROMISE score) or adding a biological marker (biological PROMISE score). Clinical PROMISE includes history of chemotherapy and radiotherapy, haemoglobin, white blood cell count, C-reactive protein level, ECOG performance status, and cancer type. To use the biological PROMISE score it is only necessary to include a biological parameter, the tissue inhibitor of metalloproteinases 1 (TIMP1), which is affordable for most clinical laboratories. This contribution is, of course, of great interest and clinically relevant. It allows a more appropriate approach in individual patients with MPE in order to decide an invasive procedure or,

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contrarily, avoid these techniques. However, this study presents other findings which are intriguing for its great potential importance for detecting therapeutic targets that enable specific therapy for MPE.

In order to search for biological markers, Psallidas *et al.* (6) performed a very interesting study using high-throughput techniques. These techniques, that include proteomics, genomics, metabolomics or transcriptomics, have stimulated the discovery of biomarkers (for diagnosis and prognosis) for different diseases. Psallidas *et al.* (6) search for pleural fluid biomarkers by using proteomic analysis (immunodepletion followed by gel-aided sample preparation) and liquid chromatography-tandem mass spectrometry (LC-MS/MS). With these methods, more than one thousand proteins were identified in the pleural fluids. An elevated number of proteins were able to differentiate between patients with different prognostic characteristics, especially in terms of survival, when two different clusters were clearly separated.

Very importantly, Psallidas *et al.* (6) reported eight proteins with potential therapeutic use on basis of their biological role. Four biological factors that could be used as therapeutic targets: TIMP1, gelsolin (GSN), versican (VCAN) and macrophage migration inhibitory factor (MIF) that are associated with survival. And also, they discovered four molecular pathways with potential clinical impact: secreted phosphoprotein 1 (SPP1 or osteopontin), fibulin 3 (FBLN3), interleukin 4, hypoxia-inducible factor 1 alpha (HIF1α) and platelet-derive growth factor (PDGF).

These four biological factors proposed as a potential therapeutic target are proteins known to intervene in carcinogenesis. TIMP1 is a glycoprotein that regulates the pericellular proteolysis of different matrix and cell surface proteins. Human cancers show consistently TIMP deregulation, and it has been demonstrated that the progression of cancer and its poor prognosis is associated with TIMP1 overexpression (7). The role of gelsolin is not yet clearly established. However, it is known that gelsolin has closely interacted with the oncogene NF-κb (8). Versican, that regulates several cellular processes (as are cell adhesion and proliferation, apoptosis, cell migration, or angiogenesis) is a large extracellular matrix proteoglycan that accumulates in tumour stroma. This protein takes part in malignant transformation and in the progression of cancer (9). Macrophage MIF is a glycoprotein that interacts with several cellular signalling pathways, causing abnormalities in homeostasis. In almost all human cancers it is possible to find high levels of this inhibitory factor. The production of MIF induces the production of chemokines, cytokines and angiogenic factors that stimulate the growth of tumours (10).

The other four possible therapeutic targets (molecular pathways) for MPE described by Psallidas *et al.* (6), SPP1 (osteopontin), fibulin 3, interleukin 4, HIF1α and PDGF, are also well-known biological markers related with cancer, and, in some cases, already used as a therapy targets in cancer patients. Osteopontin is a cytokine that intervenes on cell proliferation, cell survival, induction of drug resistance, and facilitates invasion (11). Fibulin-3, which has been already proposed as a biomarker for mesothelioma, is a member of the extracellular matrix proteins (12). Hypoxia-inducible factor 1, α-subunit (HIFI-α) participates as a basic modulator of polycomb repressive complex 2 (13). Platelet-derived growth factors (PDGF), one of the growth factors that regulate cell division, acts mainly in cells of mesenchymal origin, and is involved in cell proliferation, cell survival and migration (14).

For an adequate treatment of MPE is necessary to understand the mechanisms of its production. However, to date, the knowledge of mechanism that participate in induction, progression, resistance to therapy, and survival prognosis in MPE are poorly understood (6). But, it is known that for the establishment of tumour foci on pleural space, cancer cells need to adhere to the pleural mesothelial tissue, avert the anti-tumour host immune response, be able to invade the tissue and obtain nutrients and growth stimuli (1). MPE formation is produced by a complex interplay establishing a host-to-tumour signalling through mechanisms that stimulate pleural inflammation, tumour angiogenesis and vascular hyperpermeability. The action of these mechanisms results in the development of MPE and the possible induction of drug resistance (15,16). This fact reflects a trafficking of immune regulating cells within the tumour environment (17); consequently, the immune cell composition of pleural effusion is greatly dynamic, and cannot be considered an automatic reflect of the cellular composition of tumour tissue. Furthermore, this cellular composition in influenced by treatment, and this would imply obvious important consequences when considering individualized precision drug therapy (including immunotherapy) based on finding from cellular or biomarkers form pleural effusion.

The progress in cancer treatment in the last decades has obtained a clear improvement in cure and survival in this disease (18). However, this is not true for MPE. All these potential therapeutic targets reported by Psallidas *et al.* (6)

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imply a new possibility for the future treatment of patients that currently have not options of curative therapy. At present, the treatment of MPE is disappointing. As above-mentioned, despite the continuous progress in cancer treatment, the management of MPE remains palliative, with a median survival of affected patients below 1 year (1,2). To identify new therapeutic targets can modify substantially the approach to patients with MPE, offering the possibility of treatments that potentially extend survival and improve quality of life. Even more, using high-throughput techniques on malignant effusions, establishing mutational status at diagnosis and informing treatment resistance during targeted therapy, comprehensive profiling with different targets may be individually identified, offering a personalized treatment option.

In summary, the study by Psallidas *et al.* (6) offers results that are really exciting. On one side, brings a new score that facilitates clinical decisions regarding the individualisation of pleural procedures available. On the other side, this study opens a new opportunity for precision therapy by designing drugs based on biological findings of high-throughput techniques.

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