Editorial

Malignant pleural mesothelioma: some progress, but still a long way from cure

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In a recent issue of *Annual Reviews of Medicine*, Drs. Wald and Sugarbaker look at new concepts in the treatment of malignant pleural mesothelioma (MPM) (1). It is fair to say that in the past decade significant progress have been made in understanding the tumour biology of MPM and in developing new therapies. MPM is a rare cancer linked to asbestos exposure, for which there is no known cure (1). It is now widely accepted that asbestos causes chronic irritation of the mesothelial surface, leading to local inflammation, scarring and ultimately malignant transformation (2). In recent years, other factors such as a history of external beam radiation or genetic predisposition due to familial or de novo mutations have been identified (1).

Different types of MPM have been identified including epithelioid, biphasic and sarcomatoid with increasingly aggressive behavior and worse prognosis (1). Recently, the WHO has identified different proliferation patterns in the epithelioid type, associated with variable prognosis (3). The pleomorphic subtype is thought to be particularly aggressive with a median survival comparable to the sarcomatoid type. At the other end of the spectrum, the well-differentiated papillary epithelioid mesothelioma is thought to confer a much better prognosis and has been reclassified by the WHO as a good prognosis malignancy (3). Recently, scientists studying gene-expression-based clustering have suggested including genomic data into the WHO classification as gene-based classification and prognostication seems to be more accurate than morphology and immunohistochemistry-based classification (4). Recent studies have showed that the genomic landscape of MPM is complex (4). A recent study using next-generation sequencing (NGS) showed that the number of genomic alterations per patient ranged from 1 to 5 (median 3) and that no two patients had identical molecular portfolios suggesting that genomic analysis and personalised medicine may be warranted in MPM (2). The most common aberrations are in the genes BAP1, NF2, CDKN2A/B, TP53. In theory, some of these aberrations should be amenable to targeted therapy with PARP inhibitors, mTOR inhibitors or other newly-developed drugs (2).

Establishing the diagnosis of MPM is key as other conditions—including non-malignant diseases- can mimic MPM (1). It is now well accepted that pleural cytology is often unreliable and a proper pleural biopsy is necessary in the vast majority of patients to confirm the diagnosis and decide on the best therapeutic options. Although thoracoscopic biopsies or open pleural biopsies are good to establish a diagnosis of MPM, they only represent a small print and up to a third of patients are finally diagnosed with a different MPM type or subtype when the whole pleural specimen is examined (5). MPM is often a heterogeneous tumour and in our experience it is common to find different tumor clones in pleurectomy specimens. This may account in part for failure of targeted monotherapies as various molecular pathways are involved in the proliferation of different malignant cell populations. PET-CT has become a valuable diagnostic and staging imaging modality in MPM (6). Tumor thickness, tumor volume, tumor FDG

(fluorodeoxyglucose) uptake and total glycolytic value measured by PET have been used to predict patients' outcomes (1). However, it is far from perfect for evaluating mediastinal, diaphragmatic infiltration and thoracic lymph nodes involvement. Final histopathological staging often differs from preoperative staging and indeed a fraction of patients still undergo futile thoracotomy due to inaccurate preoperative imaging evaluation.

Many treatments have been tried to cure mesothelioma. Those have included extirpative surgery, systemic chemotherapy, external beam radiotherapy, immunotherapy and more recently targeted therapy (1). As most countries in the western-world have banned asbestos and the latency between asbestos exposure and the development of MPM is generally 25–40 years, new MPM cases are essentially diagnosed in patients over 60 (7,8). This is certainly a fact to bear in mind when proposing new therapies. A large proportion of patients have co-morbidities and are not fit for aggressive surgical procedures. Thus, for many patients a non-invasive thoracoscopic procedure such as talc pleurodesis or insertion of an indwelling pleural catheter is often the cornerstone of treatment and offers good palliation in patients who have limited life expectancy. The recently published MesoVATS study showed a 1-year survival just over 50% in patients treated by VATS pleurectomy or talc pleurodesis (9). In the national UK mesothelioma audit and in a recent European study, only 37% to 60% of patients could receive palliative chemotherapy (7,8).

The median survival of patients with MPM is around 8 months with best supportive care only (10), 12 to 19 months when systemic chemotherapy is used with or without anti-angiogenic agents or targeted therapy (1). The standard of care recommended for MPM is palliative chemotherapy based on a doublet of platinum salt and an anti-folate (1). This was established in two large randomized trials published in 2003 and 2004 looking at pemetrexed and raltitrexed in association with cisplatin (11). Unfortunately, objective response rates are 17–40% and duration of response is limited (1). Recently, the MAPS study showed a modest survival benefit—less than 3 months—in patients receiving the anti-angiogenic agent bevacizumab in association with pemetrexed and cisplatin (12). Other investigative agents targeting VEGF receptors, PDGF receptors or FGF receptors are currently under investigation in MPM following encouraging results in early phase trials (13). Maintenance therapy with chemotherapy agents (pemetrexed) or anti-angiogenic agents (e.g., bevacizumab, nintedanib) may prove useful in patients showing objective response, but life expectancy remains limited. It is reasonable to be optimistic. However, in the past decade, two large randomised studies failed to show a survival advantage with the anti-angiogenic agent thalidomide and the HDAC inhibitor vorinostat (14,15) and many promising studies involving targeted agents failed as well (16,17).

Building on successes observed in other cancers, immunotherapy based on immune checkpoint inhibitors is now being tested in MPM. Anti-CTLA-4 showed encouraging results in early-phase trials, but failed to show a survival advantage as second-line therapy in MPM (18). Anti-PD-1 and anti-PD-L1 antibodies (e.g., pembrolizumab, nivolumab, avelumab) are currently being tested in several trials in MPM. Early phase trials have showed encouraging results with objective response rates up to 28% disease control rates up to 76% and median duration of response of 12 months (19,20), but confirmatory data are needed to validate immune checkpoint inhibitors as the second line treatment of choice in mesothelioma. Combination trials and neoadjuvant trials are also planned to determine the optimal use and timing of those drugs. Other immunotherapy approaches have included anti-mesothelin chimeric antibodies (amatuximab), antibody conjugates (anetumab ravtansine), anti-WT1 vaccine, oncolytic viral therapy, dendritic cell-based vaccines and chimeric antigen receptor T cell therapies (1,21-25). Large confirmatory trials are ongoing and it will be interesting to see in the future how immunotherapy could be incorporated within multimodality protocols (e.g., with cytoreductive surgery or radiotherapy) to prevent or delay tumor recurrence following maximal cytoreduction or complete response.

In patients with early-stage disease and those fit enough to tolerate a thoracotomy, it is thought that cytoreductive surgery may offer a longer survival and an acceptable quality of life (1). The role of surgery in mesothelioma has long been a matter of debate. For more than five decades, thoracic surgeons have offered a variety of surgical procedures of which the two main are extrapleural pneumonectomy (EPP) and pleurectomy/decortications (P/D) (26). EPP is a major procedure where the lung is removed en-bloc with its pleural envelope together with the hemi-diaphragm and pericardium, whereas P/D is a lung-sparing procedure in which the pleural tumour is removed only, sometimes with the hemi-diaphragm and/or pericardium if those structures are significantly involved by tumor (1). Many institutional retrospective trials have been

published in the past two decades, claiming that radical surgery could extend survival. However, proper randomized studies comparing radical surgery and chemotherapy versus chemotherapy only are lacking (27). If surgery is to be used in the future, it has to provide a clear survival advantage or/and quality of life advantage over systemic therapies. The MARS feasibility study showed that EPP and chemotherapy did not offer a survival or quality of life benefit over chemotherapy only (27). However, this study was a feasibility trial not adequately powered to answer the question of superiority and a large proportion of patients (23%) crossed-over from one group to another, making conclusions impossible. Recent publications have emphasized the safety of EPP at expert centres, with 30-day mortality rates approaching 5%, but significant complications still occur in more than 50% of patients (28). In the past decades, many thoracic surgeons have turned to P/D as it is associated with lower mortality and less complications. Five-year survival rates of 30–35 months have been reported when P/D is used with intrapleural adjuncts such as heated povidone-iodine, hyperthermic chemotherapy or photodynamic therapy (29-31). A large phase III randomized study (MARS2) is currently recruiting patients in the UK comparing P/D and systemic chemotherapy versus chemotherapy only. In the past decade, many thoracic surgeons have abandoned EPP and adopted lung-sparing P/D based on the fact that neither procedure can achieve complete microscopic resection with clear surgical margins. In fact the IMIG guidelines recognize that the best one can aim for is macroscopic complete resection (MCR) or maximal cytoreduction (32). Then, why offer a more invasive procedure associated with higher mortality and more complications? If surgery is to be offered more liberally to mesothelioma patients, it should be an acceptable procedure that should be safe and can be tolerated by most. EPP is clearly not an operation to be offered routinely by all thoracic surgeons in all thoracic units. It is technically demanding and life-threatening complications are not uncommon, making this procedure not safe outside of an expert centre. Should EPP be definitely abandoned then? Well, outside of an expert centre and as a default procedure for most mesothelioma patients, the answer is clearly yes! However, for younger and fit patients with epithelioid (non-pleomorphic) mesothelioma, not so sure! The recently published SMART study published by de Perrot *et al*. show that in carefully selected patients, induction accelerated radiotherapy followed by EPP (within 8 days) is relatively safe and leads to good mid-term results with a median survival of 36 months (33). de Perrot has recently updated his series and showed than in more than 100 patients, 30-day mortality was 1.6%, 90-day mortality 3% and median survival over 50 months in patients with epithelioid histology (Marc de Perrot, personal communication, French National Mesothelioma Symposium, Paris, November 2017). The beneficial effect of accelerated hypofractionated radiotherapy in this study is thought to be through specific immune activation against the tumour (CD8+ cells) and long-term antitumor immune protection driven by CD4+ cells (vaccination effect) (34).

MPM is generally a radio-sensitive tumor and radiotherapy as long been used to palliate pain in patients with MPM infiltrating into chest wall (35). Radiotherapy was until recently used mainly as an adjuvant modality following EPP to reduce the risk of local relapse. A recent collaborative Swiss randomized study showed no survival benefit in patients receiving adjuvant radiotherapy versus no radiotherapy (35). Previous publications had shown that only a fraction of those having induction chemotherapy and EPP could receive adjuvant radiotherapy (27). Previous experiences in patients having had P/D showed a high rate of radiation pneumonitis, but recent experiences with intensity-modulated radiotherapy (IMRT) showed encouraging results (36), though tumour recurrence is still observed and survival needs to be studied in a large randomised trial. New protocols using neoadjuvant radiotherapy should be designed and we should eventually see if neoadjuvant radiotherapy could be used safely prior to P/D and lead to extended survival.

Altogether, in the past decade major advances in molecular medicine and immunology have paved the way for well-designed phase 2 studies and confirmatory phase 3 studies. Unfortunately, many phase 2 and some phase 3 studies have failed, highlighting the complex tumor biology of MPM. Genomic and proteomic analyses are underway to clarify the molecular landscape of MPM and identify biomarkers and actionable molecular targets. MPM is no longer regarded as one homogenous disease. Today, it looks more likely that patients with a well-differentiated epithelioid mesothelioma may benefit from therapies successfully used in other cancers (i.e., ovarian) sharing common molecular features, while those with sarcomatoid mesothelioma may benefit from new protocols involving surgery, radiotherapy, immunotherapy and/or targeted therapy protocols adapted from other sarcoma protocols We have come a long way from a rapidly fatal disease to an incurable cancer which can be palliated in some patients

and for which life-prolonging therapies are now available. Still, many patients are not fit for treatment or do not have access to treatment. The next few years will be critical to define which type of surgical procedure should be used in which patients and when. New drugs are currently being tested with some success. However, trials of monotherapies have been deceptive as various molecular pathways are involved in the proliferation of various mesothelioma cells. In addition, cancer stem cells could be a source of treatment failure following radical therapy and the role of tumor microenvironment is not completely understood (11,17).

The next decade will show if combining treatment modalities or different types of drugs can lead to a better prognosis. New biomarkers are desperately needed to stratify patients and identify those who will benefit from the most aggressive or expensive therapies. New therapies may come too late for elderly patients in the western world, but research is warranted as tens of thousands of mesothelioma cases will be diagnosed worldwide in this century due to continuous production, export and uncontrolled use of asbestos in the third world. We have come a long way, but the fight is far from over yet! Lastly, there is still no known preventive therapy for mesothelioma in patients with known asbestos exposure (37). Therefore, primary prevention is key and we must continue our efforts and eradicate asbestos.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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