Chapter 6

Malignant Pleural Mesothelioma and the Role of Non–Operative Therapies

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Additional information is available at the end of the chapter

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1. Introduction

Malignant pleural mesothelioma (MPM) is a primary malignancy of the pleura. The main aetiological agent is asbestos. The latency period lasts several decades, and in countries where its use was banned in the 1950's and 1960's, the incidence is expected to peak within the coming decade. However, in the many other countries it continues to be mined and used. The incidence in these countries can be expected to continue to rise.

The prognosis for MPM is dismal and the median survival from the time of diagnosis is 12 to 18 months. Current therapies are blunt weapons that are very morbid but at the same time ineffective. They have barely made an impact on the poor outcomes of mesothelioma.

In this chapter, we will review the current knowledge on mesothelioma pathogenesis, epidemiology, biology and treatment. We will focus on nonoperative therapies and the role of surgery will be covered in another chapter.

2. Epidemiology and aetiological factors

2.1. The history of asbestos and mesothelioma

Following the earliest descriptions of mesothelioma, it remained an exceptionally rare malignancy until after industrialisation. For a long time, primary pleural malignancies were so rare that their very existence was disputed [1]. In the early 1950s, a number of reports noted small clusters of MPM but it was not until the late 1950s in South Africa when Kit Sleggs noted that patients with tuberculous pleurisy from the east of Kimberly were recovering with streptomycin and isoniazid, but a number of patients apparently with the same disease from

the west of Kimberly continued to die. The pathologist Christopher Wagner observed that these patients had in fact a rare cancer of the pleura but yet without any other primary tumours, leading to the conclusion they had primary mesothelioma. In the same period, there were no mesotheliomas observed amongst 10,000 lungs examined from other areas of South Africa. This begged the question of why they were diagnosing so many of these rare tumours in west Kimberly. Wagner observed asbestos bodies in the lung beneath the tumour and surmised their association with mesothelioma, from that moment on the link was made [2]. His publication "Diffuse pleural mesothelioma and asbestos exposure in the North Western Cape Province" became the most cited paper in industrial medicine. This started a lifelong investigation into the association of MPM with asbestos [3].

Asbestos is a family of long, thin, fibrinous, hydrated magnesium-silicate crystals. The first record of its human use is from over 5,000 years ago, and Persians were known to make cloth with it that could be cleansed by throwing it into the fire [4]. They are classified according to their morphology into the straight and rod-like amphiboles, and the curly serpentines fibres. The amphiboles, which include crocidolite, amosite and tremolite, are strongly associated with the development of mesothelioma. The serpentine fibre chrysotile, believed to be less carcinogenic by some and non-carcinogenic by others, continues to be mined and sold in Canada to this day. The carcinogenicity of different asbestos preparations is also related to the fibre dimensions, with long, thin fibres being most strongly carcinogenic [5].

Asbestos is a versatile material valued for being weavable, resistant to heat, electricity and chemicals, being readily available and cheap. It is used in the building and construction, machinery, shipbuilding and transport industries, hence asbestos-related diseases including mesothelioma are mainly industrial work-related and therefore more common in males. The main cohorts with exposure are *occupational* - those working directly with the mining and preparation of asbestos (eg. mixing asbestos cement, cutting sheets, lagging) and end-users of asbestos such as builders, plumbers and shipyard workers, *paraoccupational* - in people living with people working with asbestos and *environmental* - from exposure to naturally occurring asbestos.

The background incidence of mesothelioma is approximately 1 per million, rising to 7 per million in Japan, 12 per million in the United States, 33 per million in the United Kingdom and 40 per million in Australia in a pattern consistent with the distribution of asbestos exposure. In Wittenoon, Western Australia where crocidolite was mined in the 1930s, follow-up records of 6,493 employees found MPM caused 3.4% deaths in exposed male workers [6]. The predicted peak incidence is expected to occur between 2005 and 2025 in countries which banned its use [7]. It is more common in males, and with a latency period between three and four decades [8], the median age at diagnosis is in the sixth and seventh decades, although there are instances when it can present in the second decade, often with a history of perinatal exposure.

There is an exposure dose-response relationship between asbestos and mesothelioma, both in terms of historic exposure (duration and episodes) and lung asbestos fibre content [9], [10] [11]. The risk is highest with crocidolite and amosite, and less with chrysotile. However, there is a background rate of mesothelioma, and virtually all mankind has been exposed to asbestos at some point – fibres have been found in the lungs of the general population. Because of this, it

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has not been possible to determine a threshold level below which exposure could be deemed safe [12] and this has important implications for legislation.

As of August 2012, 54 countries have banned the use of all types of asbestos [13]. For the rest of the countries, nearly all of the asbestos mined and consumed today is chrysotile asbestos. Developing countries are the highest consumers of asbestos, with China topping the list. With its rapid growth, China's production could not keep pace with its insatiable domestic appetite and needs to import a quarter of its asbestos. Russia, the world's largest producer with reserves that will last over a century, exports most of its asbestos [14]. Whilst the European Union and United States have complete bans on asbestos, Canada continues to mine chrysotile asbestos and is the fifth largest exporter of chrysotile to developing countries. This is in spite of severe restrictions on its domestic use. Although international agencies have long condemned the use of asbestos, it has been difficult to come to an agreement for an international ban. In June 2011, Canada for a third time objected to the inclusion of chrysotile asbestos under Annex III of the Rotterdam Convention.

2.2. The chrysotile controversy

The carcinogenicity of the amphiboles is now indisputable, but for chrysotile this has been fiercely debated. Most of the asbestos mined and utilised today is chrysotile, on the belief that this fibre is safe. This assumption is based on studies showing lesser biopersistence of the fibres, which is likely the result of the fibre's fragility, leading to fragmentation and quicker clearance from the lungs. Epidemiological studies which suggest chrysotile causes mesothelioma were dismissed by blaming contamination by amphiboles – the so-called 'Amphibole hypothesis' [15]. The experimental methodologies behind these studies have been questioned [16] [17] and it has become clear that even though chrysotile may be less potent at inducing mesothelioma, the heightened risks of asbestosis, lung cancer and death is still a glaring reality [18, 19].

2.3. Other implicated aetiological factors

2.3.1. Erionite and genetic susceptibility

An epidemic of malignant mesothelioma unfolded in 3 villages in Cappadocia, Turkey in the 1980's accounting for an unprecedented 50% of deaths in the region. In comparison to unaffected neighbouring villages, villages with mesothelioma also had high levels of airborne erionite, a fibrous zeolite with some similarities to asbestos [20]. Certainly, in animal models erionite is a very potent inducer of mesothelioma [21]. However, the incidence of mesothelioma in a nearby village with similar erionite levels was significantly lower, implicating other factors at play. Lineage studies have since incriminated an autosomal dominant transmission of susceptibility to fibre carcinogenesis to explain the disparity [22], but exposure to erionite itself remains the dominant driver of carcinogenesis [23].

Whilst erionite is also present in other parts of the world, mesothelioma directly attributable to erionite is still very rare [24]. Nevertheless, with a long latency period over three decades, the possibility of a future epidemic in erionite-rich areas, such as parts of America, is a concern [25].

2.3.2. SV40

SV40 is a polyoma virus which has long been studied as a carcinogen. The concerns over SV40 arose from the widespread administration of SV40-contaminated polio vaccines which were distributed worldwide in the 1960's. Certainly in the laboratory, SV40 virus has the ability to transform human cells and induce mesothelioma in experimental animals both directly, and as a co-carcinogen acting synergistically with asbestos [26] [27]. However, its relevance to clinical mesothelioma is less clear and the evidence is largely circumstantial. SV40 DNA fragments have been identified in 40 to 60% of mesothelioma samples [28] [29], but the copy numbers were exceedingly low (less than one per cell) [29]. Furthermore, there is no current treatment for SV40 infection.

2.3.3. Irradiation

Irradiation causes cancer and mesothelioma is no exception, Thorotrast is an alpha-emitting thorium dioxide radiocontrast used between 1930s and 1950s. It has a physical half-life of 10^{10} years and a biological half-life of several hundred years, and so it is retained lifelong, constantly exposing tissue including mesothelium to irradiation. Thorotrast is associated with many malignancies including mesothelioma [30]. Patients with lymphoma who underwent mantle radiotherapy represent another cohort with irradiation to the pleura. They also have a higher risk of mesothelioma compared to population with similar levels of asbestos exposure [31] [32].

3. Pathogenesis and biology

3.1. How asbestos causes cancer

Since most mesothelioma is associated with asbestos exposure, a lot of research has focused on how this inorganic fibre causes cancer. The physical properties of asbestos are more important for its carcinogenicity than its chemical composition. Many studies have confirmed that long (≥8 μm), thin (≤0.25 μm) fibres are most strongly associated with mesothelioma. Fibres of that size have aerodynamic features that are fine enough to allow them on the one hand to be deposited beyond the ciliated airways where they escape mechanical clearance, and on the other, large enough to frustrate phagocytosis by macrophages. Having been deposited, they migrate through still poorly understood pathways to the parietal pleura where they promote oncogenesis on the mesothelium. The chemical properties of the fibre are important insofar as they determine the biopersistence of the fibre. Chrysotile fibres, for example, are weak and fracture easily into shorter fibres which are easier to clear. Their apparent weak association with mesothelioma has been attributed to the fibre's lower biopersistence [33].

Asbestos is specifically cytotoxic to mesothelial cells in culture but not to fibroblasts [34], [35], therefore other processes must be involved *in vivo* to prevent cell death, promote cell survival and drive malignant transformation. The most widely accepted hypothesis invokes a chronic and genotoxic inflammatory response which over time drives tumourigenesis. As the long

fibres become deposited and transported to the parietal pleura, they are progressively taken up by macrophages. However, because of their sheer size and biopersistence, they could not be cleared effectively, markedly lengthening their dwell time at the mesothelium compared to other particulates. Furthermore, macrophages are unable to engulf the entirety of these large fibres. Such frustrated phagocytosis is a potent stimulation of the macrophage's inflammatory response which results in respiratory bursts and secretion of toxic metabolites such as reactive oxygen species, growth factors and cytokines. The asbestos fibres have also themselves been implicated in carcinogenesis through direct interference with the mitotic apparatus, and direct generation of free radicals through its interaction with mobilisable iron on the fibre surface [36]. Over a long period of time, it could be envisaged the unrelenting exposure to these mutagens and growth signals could drive neoplastic transformation.

3.2. Molecular pathogenesis

A central player which promotes mesothelial transformation is believed to be tumour necrosis factor-alpha (TNF-α). Asbestos stimulates both macrophages and human mesothelial cells to express TNF-α. TNF-α has been shown to promote mesothelial cell survival in the face of asbestos exposure *in vitro*, and the effect appears to be mediated through Nuclear Factor Kappa-light-chain-enhancer of Activated B Cells (NF-κB) [35]. NF-κB activation results in release of a p16 subunit which translocates to the nucleus to induce expression of antiapoptotic genes. Meanwhile, activated macrophages also secrete a host of other cytokines and growth factors including interleukins, vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF), as well as reactive oxygen and nitrogen species which directly causes DNA and chromosomal damage. Together, this sustained insult of mutagens and growth stimulators causes the first genetic alterations behind malignant mesothelioma.

Whilst most cancers have inactivation of the p53 and pRb tumour suppressor genes, mutation of these genes in mesothelioma is surprisingly rare [37] [38]. In contrast, over 70% of mesotheliomas have deletions of 9p21 and about 40% mesothelioma have loss of heterozygosity at the 22q12 locus [39] [40] [41] [42] [43]. 9p21 contains the INKa/ARF locus which encodes two proteins p16INK4a and p14ARF alternatively spliced from the same mRNA. Functionally, p14ARF stabilises p53 whilst p16INK4a inhibits the inactivation of pRb, thereby restricting progression through the cell cycle G1 checkpoint. Thus, mutations in the INKa/ARF locus effectively lead to loss of both tumour suppressor pathways. Positional cloning also identified the neurofibromatosis NF2 gene within the 22q12 locus, which encodes for the protein merlin. Merlin integrates signals from various adhesion molecules and cytoskeletal components and promotes cell adhesion, establishes apical polarity and mediates contact inhibition. It also has the capacity to migrate to the nucleus to modulate gene expression.

The precise mechanism of NF2 tumour suppression remains unclear [44] but it is likely to have a salient role. Whilst only 40% mesothelioma have truncations of NF2 or merlin, in the remaining cases, merlin is functionally inactivated through increased phosphorylation at Ser518 [45] and changes in microRNA expression [46]. Simultaneous loss of both INKa/ARF and NF2 appears to be important in the pathogenesis of mesothelioma. In experimental models of asbestos-induced mesothelioma, loss of the remaining NF2 allele is accompanied by the

concomitant loss of INKa/ARF [47]. Indeed functionally, loss of INKa/ARF appears to be permissive for NF2 tumourigenesis [48]. Thus, the evidence points to mutations in INKa/ARF and NF2/merlin as driver mutations central to the pathogenesis of mesothelioma. As a result of the genetic instability conferred by these tumour suppressor gene mutations, a large number of genetic lesions appear causing dysregulation of growth factor expression and signalling, angiogenesis and apoptosis, conferring on the cell the phenotype of malignancy.

4. Diagnosis

Pleural diseases are common and the causes are diverse, but there is also considerable overlap in the clinical manifestatations of these conditions. Because of this, MPM is notoriously difficult to diagnose, both radiologically and pathologically.

4.1. Radiology

Radiologically, pleural malignancy is often suspected on clinical history and an abnormal chest radiograph showing pleural effusion or thickening. Computed tomography can be helpful in distinguishing malignant from benign pleural processes [49]. Whilst direct invasion of surrounding structures is diagnostic of malignancy, mediastinal pleural thickening, nodules in the pleura and thickness >1cm predict malignancy with a sensitivity of 40-70% and specificity of 64-96%. In differentiating mesothelioma from secondary pleural malignancies, mediastinal pleural involvement and rind-like encasement of the lung shows a sensitivity/specificity of 85%/67% and 70%/85% respectively. Magnetic resonance imaging (MRI) has a similar performance to CT at distinguishing benign from malignant processes on the basis of morphology, but signal intensity is a useful additional feature which improves the ability to differentiate between the two [50] [51]. PET-CT is less helpful for the differentiation of benign from malignant pleural diseases and is more valuable in staging than in diagnosis [52]. Interpretation is confounded by inflammatory and infective pleural conditions and recent talc pleurodesis [53] [54]. Nevertheless, none of these modalities are absolutely specific so, irrespective of radiological findings, diagnosis of mesothelioma requires pathological confirmation.

4.2. Obtaining tissue for diagnosis

The mesothelium is a flattened layer of pluripotent mesodermal-derived epithelial cells on the surface of the pleura and mesothelioma can be morphologically diverse. Two main issues face the pathologist trying to establish a diagnosis of mesothelioma. Firstly, mesothelial proliferation is common in benign conditions, and differentiating benign from malignant mesothelial proliferation can be very difficult with many benign processes showing atypical features and mimicking invasion. Secondly, of the malignant pathologies affecting the mesothelium, secondary malignancies are by far the most common and mesothelioma is rare. Determining that a pleural malignancy is primary can also be very difficult.

The quality of tissue available to the pathologist greatly influences the ability to make a diagnosis. Fluid from a pleural effusion is helpful at narrowing the differential diagnosis but it has poor sensitivity (about 50-60%) for the diagnosis of malignancy, and in most studies the negative predictive value is around 70% [55]. However, a diagnosis may be more forthcoming when aspiration cytology is repeated [56]. For the specific diagnosis of mesothelioma, cytology has an overall sensitivity of about 30-50%, and is almost useless at diagnosing sarcomatoid mesothelioma (20% sensitivity) [57].

Tissue for histopathology can be obtained by percutaneous or thoracoscopic means. Of the percutaneous methods, the Abram's needle has the highest yield, but is only similar to cytological diagnosis [58] [59]. Although pneumothorax can be expected in 15% of patients, few require intervention and the overall complication rate is low in safe hands [60] [61]. The addition of image guidance to target areas with >5mm pleural thickening significantly improves the diagnostic yield to >80% and reduces the rate of complications [61].

Thoracoscopy allows direct visual inspection and target selection, at the same time enabling greater amounts of tissue to be obtained, thereby improving the diagnostic yield for malignancy to about 95%. Video-assisted thoracoscopy requires a general anaesthetic and single lung ventilation and may be less suited to frail patients, however, it offers the opportunity to proceed to other procedures such as opening up loculations, pleurodesis or insertion of an indwelling drain in case of trapped lung.

Thoracotomy and pleural excision remains the gold-standard for diagnosis of mesothelioma. Whilst pleural biopsy, both open and close, have a high sensitivity for the diagnosis of mesothelioma, the sensitivity for the determination of tissue subtype is approximately 80-86% and is less accurate for non-epithelioid subtypes [62] [63].

4.3. Differentiating benign from malignant mesothelial proliferation

The separation of benign from malignant mesothelial proliferation can be extremely difficult. Most processes that affect the pleural space, from pneumothorax to thoracic surgery, pulmonary diseases to systemic diseases cause a degree of pleuritis with a degree of reactive mesothelial hyperplasia. This hyperplasia can be accompanied by quite florid cytological atypia, sometimes more florid than seen in some mesothelioma. Therefore, cytological features of a specimen are not helpful in the diagnosis of malignant mesothelioma [64].

Whilst invasion necessarily implies malignancy, benign processes in the pleura can also produce features that mimic invasion. To demonstrate invasion requires surrounding fat and stroma within the biopsy specimen, that is a reason why the diagnostic yield is higher with larger surgical specimens which contain the full thickness of the pleura and the deeper surrounding tissue. To illustrate the difficulty in clinching a diagnosis, even expert members of the US-Canadian Mesothelioma Reference Panel disagree 22% of the time on selected cases referred to them [65] [66].

Some benign histological features can appear ominous, one such is entrapment, where organising pleuritis within the pleural space overlying a pleural surface gives the deceptive appearance of mesothelial invasion. This can be complicated by the concomitant appearance

of fat-like spaces within the organising pleuritis further giving the appearance of fat invasion [67]. Reactive proliferation of the surrounding stroma fibroblasts and spindled mesothelial cells can resemble sarcomatoid mesothelioma, whilst dense, fibrous pleuritis with low cellular content can resemble desmoplastic sarcomatoid mesothelioma.

Because of the difficulties differentiating benign from malignant mesothelial cells on morphological grounds, other techniques have been developed to this end. Unfortunately, immunohistochemistry is of limited value, with poor sensitivity and specificity [68], but the identification of mutated genes may be more fruitful. The discovery that the majority of mesothelioma has loss of 9q21 led to the recent development of fluorescence in-situ hybridisation techniques looking for homozygous deletions of the p16INK4a gene. Loss of p16 in this assay appears to be 100% specific for mesothelioma [40] [69]. Another avenue which has found commercial application is diagnosis through the pattern of downregulation of specific microRNAs [70].

4.4. Differentiating MPM from other pleural malignancies

Immunohistochemistry is indispensable for the differentiation between primary pleural mesothelioma and secondary malignancies. A number of markers for each of mesothelioma and the carcinoma should be used to improve the diagnostic specificity. The International Mesothelioma Interest Group (IMIG) recommends the use of at least 2 mesothelial markers and 2 markers of the tumour under consideration, and if no diagnosis could be arrived at, an expanded panel could be used [64]. Epithelioid mesothelioma markers include Wilms Tumour 1 (WT-1), calretinin. cytokeratin 5 or 5/6. Thyroid transcription factor-1 (TTF-1) is useful for the differentiation of lung adenocarcinoma, whilst CYFRA 21-1, SCCA and p63 are useful squamous cell carcinoma markers. Markers can also be selected for secondary malignancies of other tissue origin.

4.5. Histological subtypes

Many subtypes of mesothelioma have been described, but a single tumour can harbour several subtypes, so they are best broadly grouped into three types: epithelioid, sarcomatoid and mixed or biphasic. The epithelioid type is the most common (60%) whilst the other two types comprise 20% each [71]. The histological type not only determines the main differential diagnoses, but is also a predictor of response to treatment and one of the most powerful prognostic predictor [72] [73] [74].

5. Clinical features

The symptoms of MPM typically present insidiously with vague symptoms [75]. The characteristic symptoms are pain in half the patients, breathlessness in a third, and constitutional symptoms in less than 10%. At the beginning, symptoms are usually ill-defined and mild, but as the disease progresses, the initial heaviness becomes an ache and pain that interferes with

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sleep, and the breathlessness would often force the patient to stop working. Medical attention is usually only sought after a median of 3.5 months of progressing symptoms [76].

Physical examination is helpful insofar as suggesting a pleural effusion or pleural thickening, but is nonspecific for the diagnosis of MPM. Peripheral stigmata of pulmonary diseases such as clubbing and hypertrophic pulmonary osteoarthropathy are not features of MPM, and palpable lymphadenopathy is rare.

In those with large effusion, drainage may lead to rapid improvement of symptoms but a trapped lung is also common. As the disease progresses, less fluid is produced and there is progressively more pleural thickening, eventually the fluid disappears and the chest becomes contracted and filled with tumour. Local invasion of the chest wall can result in intractable pain and paresthesia, whilst invasion of the contralateral pleural space, pericardial space or through the diaphragm usually herald a rapid deterioration. Distant spread is common but is usually less symptomatic than the primary site.

The outlook for patients with mesothelioma is bad. For patients who present asymptomatically on a chest radiograph, the median survival is 20 months with best supportive care [76], and it is with this baseline in mind that we should evaluate noncomparative studies on new therapies.

6. Staging of mesothelioma

The purpose of staging is threefold: it allows stratification of patients by the anatomical extent of disease into groups with similar prognosis, enables comparison of results between studies and facilitates treatment decision-making by determining the role of specific therapies in these subgroups. However, the staging of mesothelioma is hampered by two difficulties, firstly it has a non-spherical and non-concentric plate-like growth pattern and secondly, there is a lack of understanding of the natural history of mesothelioma. This is reflected in the fact there has been six different staging systems over the last 30 years [77] [78] [79] [80] [81] [82] [83]. Only the later systems adopted the TNM model, and most have not been independently validated.

The lack of an organ within which mesothelioma grows and the way it encroaches insidiously onto contiguous structures make clinical staging by imaging challenging. This is particularly the case with T-staging. The latest International Mesothelioma Interest Group (IMIG) staging system recognises that mesothelioma starts on the parietal pleura (T1a), and the spreads onto the visceral pleura as isolated and scattered foci (T1b), which becomes confluent (T2). These features are not easily resolvable on imaging and require direct visualisation with thoracoscopy or open surgery. Nevertheless, most tumours present at the T3 and T4 stages. Here, the preoperative determination of invasion into the chest wall, mediastinum, diaphragm or pericardium is crucial to the separation of potentially resectable (T3) from unresectable (T4) tumour, but in practice this is not an exact science. The visual distinction between a contiguous structure and an invaded structure can be a difficult call. When compared to the pathological stage, both CT and MRI have an accuracy of only 50-60% in most categories, but MRI may be marginally more superior in the diagnosis of diaphragmatic and chest wall invasion on account of the signal changes in these structures [84].

Nodal metastases portends a grave prognosis in patients with mesothelioma who underwent resection [80] [85] and so accurate staging of nodal involvement is crucial for the selection of patients for radical treatment and prognostication. However, several factors complicate the assessment of nodal disease. Firstly, our knowledge of nodal staging is hampered by the fact that bronchopulmonary nodes are not routinely sampled in radical pleurectomy-decortication, or routinely reported in extrapleural pneumonectomy specimens. Secondly, the current IMIG staging system adopted the lung cancer nodal classification for mesothelioma. However, early anatomical studies has already showed that lymphatic drainage of the pleura occurs first to the chest wall (internal mammary) and paravertebral lymph nodes, whilst there is little flow upstream through the lung parenchyma to the N1 stations [86]. Indeed, the survival of patients with N1 disease does not appear to be any better than those with N2 disease [87] [88] [89] whilst the extramediastinal nodes (internal mammary, pericardial, diaphragmatic) are associated with better prognosis [90]. Finally, within the mediastinal nodes there are differences in outcomes: involvement of upper mediastinal nodes is associated with worse prognosis [90]. This is compatible with the hypothesis that mesothelioma starts basally and progresses apically.

Radiologically, the nodes are frequently obscured by the pleural thickening, and there is little correlation between nodal size and disease involvement in mesothelioma [85], so that imaging modalities based on structural criteria perform poorly at discriminating between involved and uninvolved nodes. CT and MRI has an accuracy of about 50% for nodal staging and so cannot be relied on [84]. For this reason, functional imaging such as PET and PET-CT have been investigated for their role in staging. PET alone has poor spatial resolution, but when combined with CT, increases the specificity of the PET and the sensitivity of the CT. PET-CT is more accurate for staging resectable disease than CT, MRI or PET, through its ability to diagnose distant metastases [91]. For nodal staging, the accuracy for mediastinal nodal involvement in PET-CT is about 60-66% [92] [93], therefore invasive techniques such as mediastinoscopy are still required for accurate nodal staging given its potent impact on prognosis [90]. In practice, in a population with a 'resectable tumour on CT' and mandatory mediastinoscopy, PET-CT was able to prevent futile surgery in an additional 29% patients [92].

The current staging system has several deficiencies. Firstly, it was developed with surgical patients in mind and requires intraoperative and pathological assessment. As a result, clinical staging is highly inaccurate and correlates with pathological staging less than 50% of the time [89]. Secondly, it successfully stratifies survival in only some [94] and not other surgical series [83]. Thirdly, most patients end up belonging to stage III with little differentiation within. Fourthly, it does not predict survival in nonsurgical patients such as those following chemotherapy alone [95]. There are other prognostic factors which are more powerful at stratifying prognosis of mesothelioma patients. Cell type is an important prognostic determinant, the hazard ratio for death following trimodality therapy is several fold higher than nodal status and overall stage [83] [95].

Numerous other prognostic factors have been found to be associated with survival in mesothelioma. They include *clinical factors* such as age, performance status and asbestos burden, *laboratory indices* such as haemoglobin, platelet count, white cell count and serum lactate

dehydrogenase, and *biomarkers* such as mesothelin and megakaryocyte potentiating factor [96] [95] [97]. These have been variously combined into different prognostic scores. Amongst the various scores, different factors take on different prognostic significance in different series and ultimately, the few consistent predictive factors are age, performance status, histology and stage. A gene ratio based test for molecular staging using the relative expression of four genes, namely *TM4SF1, PKM2, ARHGDIA*, and *COBLL1*, has been described and internally validated in a prospective patient set from the same institution [98]. This test was more powerful at predicting overall survival than either histology or lymph node involvement, and when combined with these, was able to differentiate three subgroups with very different outcomes [99]. Nevertheless, the test suffers the same limitation as the current staging system in its requirement for pathological data following resection.

7. Assessment of treatment response

Many tumours grow as spherical masses and linear measurements which correlate well to tumour volume can usually be taken on cross-section imaging for the assessment of response to treatment. The sheet like growth pattern of MPM over many different topologically complex surfaces meant objective measure of mesothelioma responses is difficult and subject to significant interobserver variation, the standard criteria for response assessment may therefore be unsuited to it.

The WHO criteria was introduced in 1979 to determine whether there was a complete response, partial response, stable disease or disease progression [100] and was based in part on evaluation of breast cancer response by palpation. Without stipulating the assessment protocol or measurement process, it proposed taking bidimensional measurements and obtaining the product of the longest tumour diameter with the greatest perpendicular measurement. This led to significant variation in the assessment method, and made comparison of reporting from different trials difficult. The Response Evaluation Criteria In Solid Tumour (RECIST) guideline was proposed in 2000 to try to address some of these problems [101]. It moved onto unidimensional assessment and measured changes in the longest tumour diameter on standardised imaging protocols. However, for tumours like mesothelioma, the choices of longest tumour diameter are many and subject to interpretation and bias. To improve on this, a modification of the RECIST criteria for mesothelioma was proposed to assess response by summating the perpendicular thickness of the tumour rind in two positions at three levels into a unidimensional measurement, and repeating the measurements at the same position [102]. Where appropriate for a lesion, bidimensional assessment can still be used. Within this system, a complete response is defined as complete disappearance of all tumour, a partial response by at least 30% reduction in the measurement on two occasions 4 weeks apart, progressive disease as increase in the measurement by 20% or appearance of new lesions, and stable disease as those who fulfilled neither the partial response nor progressive disease criteria.

This system was validated and showed correlation to lung function and survival outcomes [102]. Nevertheless, there is still significant overlap in survival between those with stable

disease and those with partial response, even following optimisation of the cut-off criteria for each group [103]. This has significant implications for the clinical relevance of studies which use response as their primary outcome measure instead of survival.

8. Treatment

8.1. From single to multi-modality treatment

The results of mesothelioma treatment in the 1970s and 1980s were disappointing. Radical surgery alone was associated with high morbidity and mortality, whilst its impact on long term outcomes was questionable [77]. The response rate to chemotherapy was poor amongst most agents and responses were not durable with 80% of patients developing recurrent disease within 2 years. Mesothelioma cells are radiosensitive in the laboratory [104], but the use of radiotherapy to treat mesothelioma was associated with significant toxicity resulting from the extensive volume that needs to be treated and the proximity of vital organs. The disease burden is great from both local progression and distant metastases, but none of the modalities when used alone were effective. In 1980, Karen Antman at the then Sidney Farber Cancer Institute in Boston, proposed the combination of resection with radiotherapy and systemic chemotherapy in limited disease to maximise local control and minimise distant relapse.

Studies of surgery alone have reported that following extrapleural pneumonectomy, local recurrence occurs in a third of patients and distant recurrence in half the patients [105] [106]. Therefore, there was room to improve local control, but systemic control should also be part of the treatment for all patients. Early work focused on adding adjuvant chemotherapy and postoperative radiotherapy after EPP, but compliance with early chemotherapy following lung resection was often poor due to a prolonged postoperative recovery [107]. With this in mind, and the discovery of significant responses from platinum doublets, the Swiss investigators adopted a strategy of neoadjuvant chemotherapy followed by surgery and hemithoracic radiotherapy to ensure all patients received systemic treatment [108]. They showed that surgery after neoadjuvant chemotherapy was safe and outcomes were at least comparable if not improved. With this strategy, compliance with chemotherapy was near 100% and overall compliance with all three treatment modalities was 60-70% [109].

Since then, each of the therapeutic modalities have undergone refinement and a number of groups reported improved outcomes in selected patients undergoing multimodality treatment when compared to historical results. This has led to a number of randomised trials designed to tease out the role of various components of multimodality treatment.

In this section we will review the current state of knowledge on the treatment of mesothelioma. The role and nuances of surgery will be covered in another chapter, and here we will focus on radiation therapy and systemic treatment. We will review the roles of these treatments in palliation and as part of multimodality therapy with radical intent.

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8.2. Symptom palliation

The symptoms of mesothelioma are severe and debilitating, leaving many patients miserable for their remaining time. In particular, the severity of pain and breathlessness exceeds that in non-small cell lung cancer patients [110].

Early on in the disease, breathlessness is due to pleural effusion compressing the lung and can be managed effectively by drainage. If the lung reexpands following drainage, pleurodesis can prevent reaccumulation. Most studies concern the management of malignant pleural effusions in general which include some cases of mesothelioma. Randomised trials for the use of sclerosant (drainage alone vs drainage with sclerosant), between different sclerosants and between techniques (bedside vs thoracoscopic) for malignant pleural effusions in general favoured the use of talc pleurodesis and thoracoscopy [111] [112]. One subsequent large randomised trial did suggest equivalence between bedside talc slurry and thoracoscopic talc pleurodesis [113], but the frequent need to obtain tissue for diagnosis usually favours the thoracoscopic approach. The recurrence rate following thoracoscopic pleurodesis remains however at 20-30%.

As the disease progresses, a trapped lung develops where the visceral tumour forms a constricting cortex over the lung preventing pleural apposition. Talc pleurodesis in such situations risks infection from long term drainage and contamination of a fixed space. VATS pleurectomy and decortication has been advocated as a palliative procedure which does not aim for complete macroscopic clearance, but tries to achieve lung reexpansion. There seems to be some short-term improvement in pain and dyspnoea [114] without detriment to survival [115] [116]. Recruitment to the randomised trial for VATS decortication (MesoVATS) has now closed, and the results should be available in the near future [117].

Recently, the use of long term tunnelled pleural catheters for effusions with underlying trapped lung has shown promise with very short hospital stay, low morbidity and better patient tolerability. It compared favourably with bedside talc slurry [118]. Even in patients with trapped lung, long term drainage could ultimately result in pleural symphysis, and the drain could eventually be removed in a fifth of patients [119]. Furthermore, chemotherapy can safely continue in the presence of such drains.

As the disease progresses, the effusion disappears and is replaced by a constricting tumour and a contracted hemithorax. Management of breathlessness at this stage is difficult. A palliative pleurectomy could be performed to relieve the restriction on ventilation and chest wall pain but there is significant morbidity associated with such an extensive operation. On the other hand, self-help breathlessness management techniques and opioids can help to relieve the sensation of dyspnoea.

Pain is also a significant symptom that could be difficult to manage. In addition to the WHO pain ladder, radiotherapy can improve chest wall pain in 50-60% patients [120] although unfortunately in most cases the relief is not sustained [121]. There is some suggestion that hyperthermia may increase the response rate to radiotherapy for pain control [122]. In addition, there is a significant neuropathic component to the pain, so early referral to a specialist pain management team may help to improve the quality of life in the final months.

The question of whether palliative chemotherapy has additional benefit on top of best supportive treatment was addressed by a three-armed randomised trial [123]. This was an important landmark - whilst there were numerous phase II trials addressing different chemotherapy agents, prior to this trial there were no randomised evidence to show that chemotherapy was beneficial over best supportive care, and most retrospective comparisons suffered from significant selection bias. Unfortunately, the trial experienced slow accrual and was revised to amalgamate two chemotherapy arms, which then also closed early from falling recruitment following the results of other randomised trials. This rendered it underpowered to show a survival difference. The trial was also criticised for employing non-standard chemotherapy regimens which may have led to nonsignificant results [124]. Within these limitations, it concluded the addition of chemotherapy did not improve symptoms or quality of life to any significant degree, in part because the few symptoms which improved were outweighed by the significant morbidity associated with chemotherapy.

The role of chemotherapy was indirectly addressed by other studies. The MED trial randomised 43 malignant mesothelioma (M) patients with stable symptoms to early (E) chemotherapy or to delayed (D) chemotherapy when there was symptom progression. It found patients who received early chemotherapy had a longer freedom from symptom progression and a better quality of life; furthermore, despite the small number of patients, there was a trend towards prolonged survival in the early chemotherapy group [125]. In addition to this study, a number of comparative randomised phase III studies found benefit for one regimen over another. Unless the control arms led to worse outcome than best supportive care, which is unlikely, these studies indirectly showed that a benefit for chemotherapy exists. Together, they showed that chemotherapy not only has a role in palliation as well as improving survival, but that it should be given early rather than late, and before symptoms worsen.

8.3. Chemotherapy

MPM is a particularly aggressive condition which responds poorly to treatment and chemotherapy is no exception. In the rush to make an impact, numerous studies have been carried out and almost all agents have been tried. Yet amongst these, most are small, noncomparative phase II studies, so attempts to draw conclusions about the efficacy of each treatment were frustrated by heterogeneity of the populations and variations in treatment schedules, assessment of response and reporting of outcomes, not to mention selection and publication biases. Frequently, promising outcomes in smaller trials were not replicated in larger and better conducted trials.

8.3.1. Towards cisplatin-based chemotherapy

In general, the single agent studies have been hard pressed to obtain response rates of over 20% and complete responses were rare. Of the single agent chemotherapy trials, many agents such as the vinca alkaloids (with the exception of vinorelbine) had no efficacy, and responders were few for the alkylating agents [126] [127] [128] [129]. The three classes of agents which showed some degree of response, albeit with response rates that rarely exceeded 20%, were the anthracyclines, platinum compounds and the antimetabolites/antifolates [130]. On the

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basis of this, Berghmans and colleagues carried out a metaanalysis, grouping studies into four subgroups: those which contained cisplatin without doxorubicin, doxorubicin without cisplatin, both doxorubicin and cisplatin and those that contained neither agents [131]. The composite response rate was highest for the two groups that contained cisplatin, with a higher response rate in the group that contained also doxorubicin (28.5%). On the other hand, doxorubicin alone (11.3%) was not better than trials which contained neither cisplatin nor doxorubicin (11.6%), suggesting cisplatin was the active agent.

A more recent metaanalysis [132] found the combined intention-to-treat (ITT) response rate for phase II single agent trials was indeed highest for cisplatin (20.0%) whilst almost all other classes of drugs including the anthracyclines had a rate of <10%. When used in combination, the non-platinum combination regimens had a slight improvement over single agents (overall response rate of 10.4%), but still remained some way behind single-agent cisplatin. On the other hand, certain combination therapies containing cisplatin appeared to show an improvement on single-agent cisplatin such as with anthracyclines (32.4%) and gemcitabine/irinotecan (26.1%).

These trials seemed to suggest that cisplatin is the more potent agent, and that combination therapy could improve on the results of single-agent cisplatin. Nevertheless, these phase II trials were hampered by their non-comparative nature, and the use of response rate as a surrogate outcome whilst often without reporting of survival outcomes. In fact, these responses were rarely sustained, and the link between radiological response and improved survival is tenuous.

8.3.2. The antimetabolites

Gemcitabine is a false nucleotide antimetabolite that gets misincorporated into DNA and hence interferes with DNA synthesis and repair. It showed broad activity against many solid and haematological malignancies, and has been evaluated in mesothelioma. The single agent trials were however inconsistent, with three trials showing widely differing response rates of 0%, 7% and 31% [133] [134] [135]. The overall ITT response rate was a disappointing 6.9%. There was significant heterogeneity in patient selection, chemotherapy dose and schedule, and response evaluation to explain some of the differences seen.

Cisplatin and gemcitabine are synergistic in the killing of neoplastic cells *in vitro* [136]. It is efficacious for several malignancies including non small cell lung cancer for which it became a standard of care prior to 2008 [137]. In a single institution phase II study from Australia, Byrne and colleagues administered a 6-cycle regimen of cisplatin and gemcitabine to 21 patients with confirmed mesothelioma. Tumour response was assessed by what was to become the modified RECIST criteria. There was an impressive 47.6% response rate that exceeded the results of both drugs as single agents, and a number of patients, including non-responders, found symptom relief [138]. This led to a multicentre phase II study of 53 patients using the same regimen [139]. However, the overall response rate this time was only 33% with a median duration of response of 5.4 months; the overall survival from diagnosis was a median of 17.3 months. In Europe, a phase II trial using a different dosing and scheduling regimen, obtained a response rate of 16% for the 25 patients using the WHO criteria for assessment [140].

In the absence of better phase III results, cisplatin and gemcitabine became widely adopted at the turn of the millenium and was also appropriated into multimodality regimens. In a single institution Swiss trimodality study, neoadjuvant chemotherapy with cisplatin and gemcitabine gave a response rate of 32% without increasing perioperative morbidity or mortality, and the ITT overall survival was 23 months [108]. A similar study from Memorial Sloan-Kettering Cancer Centre with 21 patients with advanced MPM reported a response rate of 26% to neoadjuvant cisplatin and gemcitabine. There were no postoperative mortality despite neoadjuvant treatment. The median survival was 33.5 months for those who completed all three modalities [141].

8.3.3. The antifolates

The other class of drugs which showed promise was the antifolate family of antimetabolites. Antifolates interfere with DNA synthesis through disrupting nucleotide synthesis, a process which requires folate. A trial of 63 patients with unresectable mesothelioma in the 1980s treated with high dose methotrexate found a 37% response rate (albeit with a looser definition of 'response') [142]. Another phase II trial of edatrexate, a drug very similar to methotrexate but for a single carbon to nitrogen substitution and greater potency, showed a response rate of 25% but with significant toxicity (20% early deaths) [143]. This required a protocol amendment with the use of leucovorin rescue. Unfortunately, this alteration also reduced the response rate.

Pemetrexed is a new generation antifolate which inhibits multiple folate-dependent processes including thymidylate synthase, dihydrofolate reductase and glycinamide ribonucleotide formyltransferase (GARFT), all of which are involved in thymidine and purine nucleotide synthesis. However, folate competes with pemetrexed for cellular uptake. Low folate levels result in higher intracellular accumulation of pemetrexed and thus higher cytotoxicity. Homocysteine levels has been found to be a marker of overall folate status and correlates clinically with pemetrexed toxicity [144]. However, a threshold level below which homocysteine levels could be considered safe could not be established. From 1999, it became a requirement to supplement folic acid and vitamin B12 in studies with pemetrexed, but trials straddling that period would include both non-supplemented and then supplemented patients.

Pemetrexed on its own showed efficacy similar to other single agents. In a multicentre phase II trial, 64 patients with confirmed MPM received pemetrexed [145], the response rate was 14.6%. Therapy was better tolerated by the supplemented patients, who also fared better with a response rate of 16.3% and median survival of 13.0 months. This was in contrast to 9.5% and 8.0 months in the nonsupplemented patients.

A large, international, multicentre, single-blinded phase III study comparing cisplatin and pemetrexed with cisplatin alone was carried out between 1999 and 2001[146]. In this pivotal study, 456 chemonaïve patients with unresectable disease or who were not surgical candidates were randomised to receive cisplatin and pemetrexed or cisplatin alone. Of these, 8 patients were randomised but were not able to receive treatment. At mid-trial, the protocol was modified to include folate and vitamin B12 supplementation to all enrolled patients. Supplementation greatly reduced toxicity: comparing patients who were never supplemented with

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those who were fully supplemented, the instance of neutropenic sepsis fell from 6.3% to 0.6%, vomiting from 34.4% to 10.7% and diarrhoea from 9.4 to 3.6%.

The trial found a significantly better response rates, time to progressive disease and survival in the combination therapy arm. The headline response rate was a remarkable 41.3% in the combination arm and 16.7% in the cisplation-only arm (p<0.0001), all responses were partial responses. However, true to the difficulty of assessing response, an independent review of imaging by the FDA confirmed only 47 of the 94 reported responses in the combination arm, but there were nevertheless still more responses in the combination arm [147].

In the final analysis, the median survival was 12.8 months in the combination arm versus 9.0 months in the cisplatin-only arm, with a hazard ratio of 0.74 [148]. Importantly, the use of vitamin supplementation did not appear to impact on the response rate or survival outcomes. On the basis of an advantage on survival, and in spite of the discrepant response rate data, pemetrexed became the first agent to be approved by the FDA for the treatment of MPM in patients whose disease is not resectable or who are otherwise not candidates for curative surgery [149].

A validated quality of life instrument (Lung Cancer Symptom Scale – mesothelioma) was also administered to all patients on the trial, and the overall symptom score was significantly in favour of the combination arm. Pain scores had worsened on the cisplatin arm but improved on the combination arm; dyspnoea scores had also worsened on the cisplatin arm but remain unchanged on the combination arm. The authors concluded that combination cisplatin and pemetrexed offered both symptomatic and survival benefit [150].

The trial was notable for its scale, rigorous execution and striking findings. However, it has also attracted a number of criticisms [151] [152]. The study was single blinded and this may have contributed to the discrepancy in observed response rates between the investigators and the FDA reviewers. There was concern that the control group was not the standard of care, ie. cisplatin doublet, but was instead single agent cisplatin which was not widely used. Furthermore, the outcome of the cisplatin-alone arm was unusually poor and this may have resulted in the combination arm appearing more efficacious. In fact, the survival benefit only reached borderline significance (p=0.051) suggesting the conclusion would have been very sensitive to small differences in outcome. The low toxicity seen in the vitamin supplemented patients may suggest that the optimal dosage of pemetrexed has not been reached, as the trial dosage was derived from the maximum tolerated dose from phase I studies carried out without supplementation.

Whilst the evidence and the FDA approval was for nonsurgical disease, on the basis of the survival benefits of the Vogelzang trial, several phase II studies of trimodality treatment adopted cisplatin and pemetrexed as their neoadjuvant chemotherapy from 2003. Krug and colleagues reported a multicentre phase II trial of 77 patients with cT1-3,N0-2,M0 histologically confirmed MPM undergoing trimodality therapy with this combination [153]. 64 patients (81.3%) were able to complete 4 cycles of chemotherapy. The radiological response rate with this regimen was 32.4%, of which 3 had pathological complete response at extrapleural pneumonectomy. The ITT median survival was 16.8 months, and for the 52% who completed

all three modalities, the median survival was 29.1 months. In a similar vein, a multicentre European Organisation for Research and Treatment of Cancer (EORTC) trial in 2005-2007 recruited 58 patients with earlier stage (cT1-3,N0-1,M0) histologically-confirmed MPM for 3 cycles of cisplatin and pemetrexed followed by EPP and radical radiotherapy [154]. The radiological response after chemotherapy was a remarkable 43.9% (24.6% complete response and 19.3% partial response). The ITT median survival was 18.4 months. 37 patients completed all 3 modalities and their median survival was about estimated at 33 months, although the median was barely reached within the follow-up period and so does not allow a confident estimate.

Another new generation antifolate which has been tested in a randomised phase III setting in MPM is raltitrexed. Unlike pemetrexed, raltitrexed is a selective inhibitor of only one folic enzyme - thymidylate synthase. In a phase II study, single agent raltitrexed gave a response rate of 20.8% with only mild toxicity, without requiring vitamin supplementation [155]. This led to a multicentre randomised phase III study of cisplatin/ raltitrexed against cisplatin alone in patients with MPM not amenable to surgical resection [156]. 250 patients were randomised between the two groups. The radiological response rates were 14% for the cisplatin-only group and 24% for combination cisplatin-raltitrexed. There was a borderline significant increase in median survival for the combination chemotherapy arm (8.8 months vs 11.4 months, p=0.048). The study also assessed quality-of-life but did not find difference in the measures between the two arms.

Aside from the scale of the trials, the magnitude of benefits seen in the pemetrexed and raltitrexed randomised trials were very similar. An economic analysis recently found raltitrexed/cisplatin to be much more cost effective than pemetrexed/cisplatin combination chemotherapy [157]. Raltitrexed however, is not available in the US, and so the standard of care there remains cisplatin with pemetrexed or gemcitabine [124].

8.3.4. Second-line chemotherapy

The response rate for existing chemotherapy is poor and many patients have disease progression during first line therapy. Even for those who respond, the improvement is not durable. This relentless progression inevitably leads to a question of second line chemotherapy. The evidence for second-line therapy is however, limited, and many studies are confounded by rampant immortal time bias – that only patients who can survive to and are fit enough to receive second-line chemotherapy will receive it, so that treatment benefits will be arbitrarily overestimated.

For pemetrexed-naïve patients, both pemetrexed and non-pemetrexed-containing regimens have been used. There is little difference between the two and the outcomes were generally poor with a median time to progression of several months. Janne et al. reported on the outcomes of the extended access program for pemetrexed on 153 pemetrexed-naïve patients [158]. Some patients received single-agent pemetrexed, and others combination cisplatin and pemetrexed. The response rate and median survival was 32.5% and 7.6 months for combination therapy and 5.5% and 4.1 months for single agent therapy. There is an element of selection bias

as patients who were older, have poorer performance status were more likely to receive only single agent therapy. They were also more likely to receive fewer chemotherapy cycles.

A multicentre phase III randomised trial also addressed the benefits of pemetrexed alone as second line chemotherapy versus best supportive care in pemetrexed-naïve patients. 243 patients were randomised, but 60% patients died or progressed on the trial treatment. The response rate was 18.7% with pemetrexed and 1.7% without, and progression free survival and time to progression were all in favour of pemetrexed. However, there was no difference in overall survival observed which may relate the large number of patients on the best supportive care arm who went onto receive early post-discontinuation therapy including pemetrexed. Quality of life was difficult to assess because of the rapid rate of attrition of these patients.

For pemetrexed-pretreated patients, both pemetrexed-containing and non-pemetrexed-containing regimens have been reported in noncomparative studies. For non-pemetrexed containing regimens, the response rates were reported as <10% and the time to progression was 2-3 months [159] [160]. Pemetrexed retreatment have also been investigated in pretreated patients. In one Italian institutional series, 31 pretreated patients were retreated at disease progression. There was a 19% response rate and a progression free survival of 3.8 months. They also noted that patients who had a longer progression free survival after first line chemotherapy also derived a longer progression free survival after second line retreatment [161], so that the ability to respond to the drug is not lost after first line treatment. In a larger multicentre retrospective observational study, the same authors reviewed 120 pemetrexed pretreated patients of which 42 were retreated with a pemetrexed regimen and 78 with a non-pemetrexed regimen. Those who received the pemetrexed regimen had a higher disease-control rate, and those rechallenged with platinum/pemetrexed combination therapy had a significantly longer progression free and overall survival than those receiving monotherapy (HR 0.11) [162].

However, the results of second line therapy remain poor and there is no standard therapy, this has made it a platform to test new agents. Many of the new targeted therapy drugs have been investigated as part of second line therapy, but this stage of the disease also places extraordinary demands on a new agent to prove a therapeutic value, and a negative trial on this platform risks writing off an effective agent.

8.4. Targeted therapy

In addition to the classical and largely indiscriminant cytotoxic chemotherapy, the landscape of oncology has recently been transformed with the arrival of targeted agents which target the many molecular alterations identified on the malignant cells. The successes of these agents in other malignancies have also led to them being tested in mesothelioma. There are many such agents, some of which have been or are investigated for mesothelioma. In this section we will outline the main targets, but the list is by no means exhaustive. The prevailing theme, nevertheless, is that the agents tested to date have not been successful.

8.4.1. Vascular Endothelial Growth Factor (VEGF)

Angiogenesis is crucial for tumour growth and mesothelioma is no exception. Indeed, angiogenesis is itself a poor prognostic factor for mesothelioma [163]. VEGF is not only a paracrine growth factor for blood vessels but also an autocrine signal for mesothelioma cells which expresses the VEGF receptors (VEGFR) -1, -2 and -3 [164]. A number of angiogenesis inhibitors are now available, and some has demonstrated effectiveness against malignancies such as colorectal cancer, non-small cell lung cancer (NSCLC) and multiple myeloma.

A number of anti-VEGF agents have been tested in mesothelioma but the results have been disappointing. Bevacizumab (Avastin) is a humanised anti-VEGF-A antibody which has showed effectiveness in metastatic colorectal cancer and NSCLC. In a phase II trial of patients with mesothelioma not amenable to curative intent surgery, they were randomised to cisplatin/gemcitabine with either bevazicumab or placebo. There was no difference in progression free or overall survival [165]. In a similar vein, the addition of bevazicumab to cisplatin and pemetrexed in a noncomparative trial did not result in improvements in response rates or survival compared to historical results [166]. A randomised trial of pemetrexed-cisplatin with or without bevacizumab is currently ongoing in Europe (MAPS trial).

Thalidomide has been resurrected in the 1990s when it was shown to be a powerful antiangiogenic agent. Clinically, it has showed effectiveness in multiple myeloma. In a dose escalation study, it was given to 40 patients with MPM irrespective of previous treatment [167]. Response was not formally reported, but only 27.5% patients were free from progression at 6 months.

Many other agents targeting the angiogenesis pathways such as sunitinib, vatalanib, sorafenib and NGR-hTNF have been tested in MPM alone or in addition to a cisplatin doublet, however, they mostly showed no or only very modest activity against MPM [168] [169] [170] [171].

8.4.2. Epidermal Growth Factor Signalling

EGF receptors (EGFR) is overexpressed in MPM. The tyrosine kinase inhibitors targeting EGFR, such as erlotinib and gefitinib, have been so successful in various types of cancer they too have been tested in MPM. Unfortunately, in phase II trials, these two agents did not show any significant activity against MPM: in both erlotonib trials, no objective response was observed [172] [173] whilst the gefitinib trial only showed a 4% response rate [174].

8.4.3. Histone deactylase inhibitors

Acetylation of histones is an important mechanism of epigenetic regulation of gene expression: acetylation frees the DNA from histones and increases gene expression, at the same time promoting cell cycle arrest or apoptosis. Histone deacetylase (HDAC) inhibitors have been developed and investigated in MPM. In the largest randomised trial in MPM to date, 660 patients pretreated were randomised to vorinostat, (a HDAC inhibitor) or placebo. The results were reported at the European Multidisciplinary Cancer Congress in September 2011. The triallists reported that vorinostat did not improve the response rate or overall survival compared to placebo [175].

8.4.4. NF-κB pathway

The NF-κB pathway is important in the pathogenesis of mesothelioma. Two agents that target the pathway have been investigated in mesothelioma. Bortezomib, a proteasome inhibitor which induces apoptosis in mesothelioma cells is currently studied in several trials [176]. In a phase II trial of monotherapy bortezomib, the response rate was 4.8%, and the majority of patients had disease progression on treatment within the first two cycles [177]. Ranpirnase is a ribonuclease found in the Northern Leopard Frog oocyte. It is a tRNase that also prevents NF-κB nuclear translocation. In a large phase II study of single-agent ranpirnase which included patients who previously did not respond to chemotherapy, the response rate was 5% and the ITT median survival was 6 months [178]. In a phase III randomised trial of doxorubicin with or without ranpirnase for both chemonaïve and pretreated patients, there was no difference in ITT overall survival. However, a survival benefit could be seen in the preplanned subgroup analysis of the pretreated subgroup [179].

9. Radiotherapy

Radiotherapy has been studied in three roles for the management of mesothelioma: the palliation of symptoms, prevention of tract site metastases and with radical intent to improve survival alone or as part of multimodality treatment. The first of these was covered earlier and we will focus our discussion here on the other two roles.

9.1. Prophylactic irradiation

Mesothelioma has been known to seed along interventional tracts to form painful subcutaneous nodules and radiotherapy is commonly used in the prevention of such metastases. In general, the more invasive the procedure, the higher the likelihood is of getting tract metastases [180]. The carte blanche to give prophylactic irradiation came from a randomised trial in 1995 [181]. Boutin et al. randomised 40 patients following thoracoscopy to local irradiation with 21Gy of 12.5-15 MeV electrons in 3 fractions within 15 days of the procedure. They found an incidence of subcutaneous nodules of 40% in the untreated patients and 0% in the irradiated patients. Since then, prophylactic irradiation of intervention sites has become entrenched in guidelines [182] [183] and clinical practice [184] [185].

Two subsequent randomised trials found an incidence of subcutaneous nodules of only about 10% of patients, and that prophylactic irradiation offered no protection against the development of these nodules [186] [187]. The interpretation of these results was confounded by different radiotherapy techniques in these trials [188]. Bydder et al. employed a single fraction of 10Gy of 9MeV electrons delivered up to 15 days following intervention, and O'Rourke employed 21Gy in 3 fractions of 9-12 MeV electrons up to 21 days following intervention. Furthermore, all three trials were underpowered, and in none of them was histological confirmation of subcutaneous nodules obtained.

Further questions which confuse the issue for prophylactic irradiation included the degree to which these nodules are symptomatic - reports varied between 25% and 75% [187] [189],

and to what degree these nodules impact on the quality of life of patients. To illustrate the confusion and debate surrounding the use of prophylactic irradiation, we need look no further than the evidence-based guidelines. The latest British Thoracic Society guideline continue to recommend prophylactic irradiation [190], whilst the European Society of Medical Oncology and the European Respiratory Society were not able to recommend it [191, 192]. In the penumbra of all this equipoise, a new randomised trial is being conducted to assess the role of prophylactic irradiation in the modern era of chemotherapy, in an adequately powered multicentre study [193].

9.2. Radical radiotherapy

Radiotherapy has been used both alone and as part of trimodality therapy in the radical treatment of MPM. A number of trials in the 1980's examined the use of radiotherapy alone with radical intent and found no survival benefit [194]. The use of radiotherapy for mesothelioma is complicated by the extensive field which it is required to covered, but at the same time juxtaposition of vital structures such as lung, oesophagus, spine, heart, liver and kidneys which limits the dose that can be delivered. Following irradiation of the hemithorax for mesothelioma, the loss of lung function is complete and equivalent to a pneumonectomy [195]. There is a real risk of treatment-related deaths, reaching 2 out of 12 in one retrospective series [196]. Because of this, it is felt radical radiotherapy should be delivered only after extrapleural pneumonectomy, to avoid the morbidity and mortality associated with life-threatening toxicity to the in-field ipsilateral lung.

The local relapse rate following surgery alone is 70-80% [105], and the focus of radiotherapy has shifted over the years to improving local control within the model of multimodality treatment. However, the rate of local recurrence from single modality radical treatment 53% [197], 35% [198] and 11% [199]. There is a suggestion of a dose-response relationship between radiation dosage and local recurrence but this has not yet been established [199] [200]. Beyond these observational series there is no randomised evidence yet to support or refute the use of postoperative radiotherapy. A multicentre randomised trial for radiotherapy within trimodality therapy is currently recruiting, but the trial will reach completion only in late 2017 [201]. At present, it is common to include postoperative hemithoracic irradiation to 54Gy within trimodality therapy.

With the tumour abutting a number of radiosensitive vital structures, there has been great interest in the use of intensity-modulated radiotherapy (IMRT) to deliver radiation in a field which conforms much more tightly to the target volume, in an effort to improve delivery to the tumour whilst reducing bystander irradiation. It is much more complex to deliver and requires significantly longer planning and treatment times. Whilst there is a growing body of evidence in support of the benefits of IMRT in various cancers, its use in mesothelioma appears to be harmful. In a series from Boston, fatal pneumonitis in the remaining lung occurred in 6 of 13 patients [202], whilst in MD Anderson, 23 of 63 patients died within 6 months of IMRT, of which 6 were from pulmonary causes [203]. The factor which predicted pulmonary complications appeared to be V20 (volume of lung receiving over 20Gy irradiation) [204]. At the same time, however, the locoregional failure rate remained at 13% [203]. Several subse-

quent series together corroborated the findings of a relationship between pulmonary complications and V20 [205] [206] [207]. As it stands, there is no evidence for additional benefit from IMRT, whilst there are significant concerns about harm. IMRT has not replaced conventional radiotherapy and its use should be confined to carefully monitored clinical trials.

Historically, EPP has been reserved for patients who are fit to undergo pneumonectomy, whilst patients who are less fit and/or have unresectable disease are often offered radical pleurectomy/decortication (P/D). However, despite this strategy, patients who underwent EPP not only have a survival advantage over those who underwent P/D, but actually had more morbidity, mortality and worse survival [208]. In recent years, the enthusiasm for EPP has waned and many surgeons has shifted to offering the less morbid P/D, to the extent that the proposed MARS2 trial intends to abandon EPP and instead randomise patients between radical P/D and no surgery [209].

The implication this has on delivering radiotherapy within multimodality therapy is significant. Whilst local control becomes even more pertinent, the risk of radiotherapy is also higher because of toxicity to the unresected lung. With the poor results of single modality radical radiotherapy, there is little experience of radiotherapy after pleurectomy-decortication. Some groups have delivered prophylactic radiotherapy to the surgical wounds with occasional boost radiation to at-risk areas, and therefore although described as trimodality therapy, these studies did not reflect the radical doses resembling that after EPP [210].

When higher dose external-beam radiation was used after pleurectomy-decortication, there was significant treatment-related mortality and morbidity. Likewise, the addition of intraoperative brachytherapy to the pleural space was associated with worse, not better survival. Nevertheless, there was some suggestion that delivery of >40 Gys was associated with better outcome although there is inevitably selection and immortal time bias [211]. There has been interest therefore in the use of IMRT after pleurectomy-decortication to improve delivery of therapeutic doses to disease area whilst keeping normal tissue irradiation to a minimum. Planning is challenging, and for MPM requires over 20 planning cycles. A phase I study found IMRT up to 50Gy was feasible but severe pneumonitis occurred in 20% patients. The median survival of 26 months after receiving all three modalities was comparable to the results after trimodality treatment with EPP [212].

10. Conclusion

In conclusion, MPM is an aggressive malignancy which presents insidiously, is difficult to diagnose and is resistant to most standard treatments. There have been a lot of developments over the years but the prognosis remains bleak. A number of ongoing current trials are looking to refine the treatment of this cancer, but it will probably take a quantum leap in thinking to really make a dent in the outcomes.

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