Personalizing treatment for malignant pleural mesothelioma

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CHAPTER 1

Introduction and Outline of this Thesis

Mesothelioma

Mesothelioma is a tumor arising from mesothelial cells lining the pleura, pericardium or peritoneum. It usually spreads locally and causes thickening of this lining, accumulation of fluid, or both, leading to symptoms of pain and dyspnea when situated in the pleural cavity, and obstipation and pain when the peritoneum is affected. If untreated, most patients die within 2 years from start of symptoms.

Asbestos

Inhaled asbestos fibers are recognized as the main causative factor for developing mesothelioma. Asbestos is a term used to describe a group of 6 different mineral fibers that occur naturally throughout the world. Two subgroups can be distinguished based on their structure: the serpentine group and the amphiboles. Serpentine refers to a green, snakelike feature seen in this type of mineral. Chrysotile (white asbestos) is a serpentine mineral and the most commonly used type of asbestos. Amongst the amphibole minerals are amosite (brown asbestos), crocidolite (blue asbestos), tremolite, actinolite and anthophyllite [1]. The fireproofing properties of asbestos were already known in prehistoric times as can be concluded from archeological findings of clay pots containing asbestos fibers to make the pots fire resistant [2]. The ancient Greeks and Romans used asbestos in cloths for various purposes. Famous examples are the wicks used by the Vestal Virgins to maintain an eternal fire burning in the temple of the goddess Vesta. Mining and weaving of the fibers was done by slaves who were known to die early. Plinius Maior, a Roman historian and philosopher described the use of a thin membrane from a goats' bladder to prevent inhalation of asbestos fibers during mining [3]. Asbestos became increasingly popular at the time of the Industrial Revolution since its resistance to heat, electricity and chemicals and its plasticity made it an ideal material to insulate the steam engines and machines that were developed at that time. To meet the need for asbestos, commercial mines were established in Canada, Russia, Scotland, England, Germany and Italy. Mining in Australia, Finland, South Africa and Zimbabwe started a few decades later. In 1899 the Austrian born Ludwig Hatschek developed a technique to add asbestos to cement and called the patented product Eternit which acquired many applications in construction [4]. The harmful effects of asbestos were already suspected in the late nineteenth century as can be concluded from a 1902 report of Lady Anderson, an English Inspector of Factories who included asbestos on a list of dusts that were known to cause harm to man [5]. Scientific proof of its injurious effects became available with publications on asbestosis, a condition first described in 1924 by the British pathologist Cooke as '*Fibrosis of the lungs due to the inhalation of asbest dust*' [6-8]. In 1949 asbestosis was recognized as an occupational disease by the Dutch government [9]; a status the British government already decided to in 1931. This recognition was necessary for a

patient to be considered for a disability allowance. The notion that asbestos had carcinogenic properties and could induce lung cancer was first published in 1938 [10]. Epidemiologic argumentations for this idea were provided by Doll in 1955 [11]. A decade later Gross published his animal experiments in which he intratracheally administered asbestos to rats and found a high percentage of lung carcinomas, a malignancy very uncommon to rats [12]. From 1960 on, it became clear that asbestos could induce not only lung cancer but also mesothelioma, a very rare disease [13-15]. The Dutch doctor Stumphius dedicated his thesis to the health risks of asbestos and analysed the employees of a shipyard and a machine factory on the island of Walcheren that had evident asbestos exposure. He found asbestos bodies in sputum and biopsies of almost all employees and an unusually high prevalence of mesothelioma.

Epidemiology

In his thesis in 1969 Stumphius warned that due to the widespread use of asbestos, mesothelioma could become a serious health threat, and asked for preventive measures [16]. It was only in 1993 that the Dutch Government banned all use of asbestos products. In 1969 90 cases of mesothelioma were registered in the Netherlands. Since then the incidence has increased more than six times. One would expect the numbers of new cases to drop since no new asbestos products are being used from 1993 onwards. But due to the extensive use in the seventies and the long latency period of 30-50 years, a peak in incidence is expected. This peak is predicted between 2015 and 2021 [17, 18]. However, since 2010, there seems to be a plateau in the Netherlands of around 550 new cases a year [19]. Globally, the mesothelioma incidence varies widely. Rates are highest in successively the United Kingdom, Australia and the Netherlands [20]. Many reasons exist for this global variation. The first reason is obviously the extent of asbestos used: countries with a high grade of industrialization consumed more asbestos. Many of these countries now have prohibited use of all types of asbestos. However, around 140 nations worldwide – mostly low-income countries- still have little or no regulation on asbestos [21]. Secondly, the reliability of the diagnosis may vary. Mesothelioma is notoriously difficult to diagnose. To improve the quality of the diagnostic process, several countries established national panels of expert pathologists that review all suspected cases of mesothelioma. The Dutch Mesothelioma Panel (Nederlands Mesotheliomen Panel (NMP)) started its work in 1969. Another factor that may explain the global variation in incidence, is the diversity in life expectancy throughout the world. The average age at mesothelioma diagnosis is 69. In Russia for example, men die at an average age of 64.7 years and may not live long enough to develop this disease [22]. Apart from asbestos, there exist many (around 390) other mineral fibers that do not fall under asbestos regulations but that are associated with mesothelioma [23]. Erionite for example, occurring in gravel that was used to pave roads in North Dakota in

the United States, is less widely used than asbestos but more potent in causing cancer [24]. Our current patients are likely to have been exposed to asbestos by working in construction, shipbuilding, or the automobile-industry (brake linings), but exposure may have occurred in as many as 70 branches of industry in the Netherlands [25]. These professions explain the male predominance of this disease.

Treatment

In cancer therapy in general, surgery is the best treatment option to achieve curation. In mesothelioma however, radical resections are extremely difficult due to the widespread distribution of the cancer in the pleural cavity. It is disputable whether treatment for mesothelioma can be curative, but if so, it needs to include chemotherapy and possibly also radiotherapy. Extrapleural pneumonectomy (EPP) -complete resection of the involved lung and pleura- has a high morbidity and non-neglectable mortality and unfortunately, the disease often recurs. Many research papers that advocate surgery describe case series of highly selected patients with a long survival, but the impact of these articles is moderate due to selection bias [26]. A recent comparison between treatment schedules including surgery and schedules without surgery using propensity matching scores, demonstrated improved survival with surgery-including multimodality treatment [27]. However, the best method to assess the value of surgery is through randomization as was done in the Mesothelioma And Radical Surgery (MARS) trial [28, 29]. The conclusion of the authors that EPP offered no benefit and could even harm patients, induced a lot of criticism but did lead to development of new trials with lung-sparing surgical procedures such as extended pleurectomy/ decortication (EPD) [30]. The potential benefit of EPD in combination with chemotherapy is currently evaluated in the MARS2 trial and the EORTC1205 trial. What is evident from surgical trials is that most patients with mesothelioma are not eligible for surgery whatsoever due to poor performance status or disease extent. In the Netherlands, chemotherapy consisting of a platin and pemetrexed combination is considered the standard of care, based on a trial published in 2003 by Vogelzang et al [31]. Surgery-including multimodality treatment is only performed in the context of clinical trials. In many other European countries and the United States however, surgery of mesothelioma is more common.

Personalized therapy

The general trend in oncology is to move from ‘one size fits all’ to personalized treatment. A personalized approach asks for biomarkers that allow selection of an appropriate drug for a certain patient. With the research described in this thesis, we aim to personalize mesothelioma therapy by combining clinical studies with translational research and

preclinical models. An overview of recently tested systemic treatments with a focus on predictive biomarkers is given in chapter 2 (*Emerging Therapies for Malignant Pleural Mesothelioma*).

Preclinical models

Conducting clinical trials in a small and frail patient population such as the mesothelioma population is challenging. Difficulty in staging and response evaluation further complicate this. Staging in mesothelioma was mainly based on surgical assessment of disease extent. Since only a small proportion of all patients undergo a surgical procedure, reliability of staging is limited. To improve this, the International Association for the Study of Lung Cancer (IASLC) has constructed a database that resulted in the 8th edition of the TNM classification for MPM published in 2016 [32-35]. In spite of these improvements, staging -and with this stratification of patients in clinical trials- remains a huge challenge. Furthermore, radiologic assessment is notoriously difficult in MPM resulting in large interobserver variation in response evaluation. Assessment of tumor volume may improve this but has not found its way to clinical practice yet [36]. Adequate preclinical selection of compounds is therefore essential to optimally use the limited patient- and medical resources for clinical trials. It is key to develop preclinical models that most accurately resemble the original tumor. Chapter 3 gives an overview of existing preclinical models (*A Catalogue of Treatments and Technologies for Malignant Pleural Mesothelioma*). Mouse models are developed by elimination of INK4/ARF that lead to rapid development of mesothelioma tumors [37]. However, most mice develop sarcomatoid tumors while in humans, epithelioid histology predominates. Therefore, we aimed to develop a model that better represents the human tumor type and simultaneously reflects the genetic diversity of the population. Chapter 4 describes our newly developed culture model of primary tumor cells derived from pleural fluid of patients with mesothelioma, the drug sensitivity assays performed with this model and the correlation with expression profiles and clinical responses (*Chemical Profiling of Primary Mesothelioma Cultures defines Subtypes with Different Expression Profiles and Clinical Responses*).

Pharmacogenomic profiling

In non-small cell lung cancer (NSCLC) the discovery of genetic aberrations such as EGFR mutations, has had major implications for treatment. At the start of this thesis, the genetic landscape of mesothelioma was largely unknown. Our aim was to explore this landscape in cooperation with the Welcome Trust Sanger Institute and search for genetic alterations that are potentially targetable. This was done by combining data from whole exome sequencing and drug sensitivity screens performed with a large panel of mesothelioma cell lines

including several primary tumor cell lines derived from our patients. Chapter 5 describes the results of this effort (*Comprehensive Pharmacogenomic Profiling of Malignant Pleural Mesothelioma Identifies a Subgroup sensitive to FGFR inhibition*).

Immunotherapy

The durable properties that make asbestos attractable for industrial applications are the same properties that cause health damage. Asbestos fibers are inert and when inhaled they move to the pleura where they remain present during a lifetime. There they cause chronic inflammation which eventually can result in neoplastic transformation of mesothelial cells. The role of the immune system in the development of this disease suggests that it may also play a role in the treatment of mesothelioma. The positive effect on survival of a large lymphocytic infiltrate in a tumor of patients with mesothelioma was noted already in 1982 [38] and spontaneous regression of mesothelioma does occur suggesting a role for the immune system. It was noted that mesothelioma patients treated with BCG vaccine immunotherapy had a better survival compared to those who only received best supportive care [39]. The positive effect of dendritic cell therapy [40, 41], has substantiated this hypothesis. The clinical results of our NivoMes trial with PD-1 inhibitor nivolumab in patients with mesothelioma, progressive after at least one line of systemic therapy, is described in chapter 6 (*PD-1 blockade with nivolumab in patients with recurrent Malignant Pleural Mesothelioma*). Translational research to find biomarkers that predict for response is ongoing and falls out of the scope of this thesis.

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