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Current efforts in research of pleural mesothelioma—An analysis of the ClinicalTrials.gov registry

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ABSTRACT

Objectives: Currently there are many uncertainties in the optimal treatment of malignant pleural mesothelioma (MPM), this is reflected in discrepancies between current guidelines. Our aim was to evaluate the current status of prospective interventional clinical trials within the ClinicalTrials.gov registry in MPM in order to predict a potential impact on MPM management in the next years.

Material and Methods: The records of 263.832 clinical trials registered were searched in December 2017. Trials starting between 2005 and 2017 (n = 262) were selected for further manual review. Trials including other tumour entities or mesothelioma originating outside the pleura (n = 94) were excluded, as well as trials where the primary endpoint has already been published (n = 22).

Results: In total, 91 clinical trials were identified and selected for further analysis. Most trials had a single arm design, were in phase I, and were non-randomized. Academic centres were recorded as primary sponsors in the majority of trials (56%), followed by industry in 21%.

Most studies investigated targeted (n = 42) or cytotoxic therapies (n = 39). Ten studies investigated different genetic therapies. In 67% of the trials (n = 61) targeted and/or cytotoxic therapies were involved.

Treatments involving surgery were investigated in 12 trials (13%), radiotherapy in 10 trials (11%).

Only five studies (6%) were phase 3 studies and one was a phase 2/3 study. Four of these five phase 3 trials investigated targeted therapies, while one trial investigated prophylactic radiotherapy of operative tracts.

Conclusions: Currently running trials in MPM are mostly in early phases and dominated by systemic therapies. Very few trials evaluate loco-regional therapeutic approaches. The current controversy surrounding the use of surgery and radiotherapy within multimodal therapy strategies will not be answered by these trials in the coming years.

1. Introduction

Malignant pleural mesothelioma (MPM) is an aggressive form of cancer arising from the mesothelial surfaces of the pleural cavity with limited therapeutic options and dismal outcomes. Overall survival (OS) is around one year after diagnosis and up to two years with intensive multimodal treatments [1–7]. Several prognostic factors have been developed for MPM. The EORTC and CALGB prognostic groups separate patients into groups with better and worse prognosis but they have been studied only retrospectively [8,9].

Treatment of MPM is highly discussed mainly when considering local therapy. For disease limited to the hemi-thorax, maximal surgical cytoreduction may be attempted with extrapleural pneumonectomy (EPP) or by a procedure classified as “pleurectomy/decortication” (P/D) [10]. Radiotherapy may lower loco-regional recurrence rates after maximal cytoreduction, but has yet to prove a positive impact on survival [11]. Based on limited evidence on the most appropriate local therapy: how to operate, whether to operate at all, and the role of perioperative radiotherapy, controversy has spilled over to recently published guidelines with discrepant recommendations from the British Thoracic Society (BTS) and the American Society for Clinical Oncology (ASCO) guidelines.

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Standard systemic therapy currently consists of cisplatin combined with pemetrexed, which can prolong overall survival in patients with un-resectable disease [1]. The addition of bevacizumab to pemetrexed/cisplatin demonstrated improved outcomes [12], while it has no market authorisation from EMA or FDA. If surgery is considered, neoadjuvant [5,6] or adjuvant [2] chemotherapy are used in multimodal treatment.

While pleurodesis, tunnelled catheters, subtotal pleurectomy, or palliative radiotherapy may be considered in symptomatic patients [13–16], targeted therapeutics [12,17–21] and intra-pleural gene therapy [22], intracavitary therapies (chemotherapy, photodynamic), among other experimental treatments, are being investigated, until now, without impact on clinical practice [23].

To obtain an overview of ongoing clinical trials in the field, we explored the ClinicalTrials.gov database, which might provide a glimpse into the future of MPM management [24,25].

2. Material and methods

An analysis of trials registered in ClinicalTrials.gov was performed, as reported for other investigations [26,27]. The records of 263.832 (100%) clinical trials registered were searched in December 2017 for all trials containing the word “mesothelioma” in the condition section. Three hundred twenty-three trials were retrieved. Trials starting between 2005 and 2017 (n = 262) were selected for further manual review. Trials labelled as Suspended, Terminated, Withdrawn or with Unknown status were excluded (n = 55). Two hundred seven trials were manually reviewed and classified. Trials that included patients with other tumour entities or including mesothelioma originating outside the pleura were excluded (n = 94). In addition, we excluded trials with a published primary endpoint (n = 22). The remaining ninety-one were used in the analysis. The selection process is shown in Fig. 1.

Every trial reported arms. An arm is defined as a pre-specified group or subgroup of participant(s) in a clinical trial assigned to receive specific intervention(s) (or no intervention) according to a protocol. Arms are categorized by the ClinicalTrials.gov into the following categories: Experimental, Active Comparator, Placebo Comparator, Sham Comparator, No Intervention and Other. An arm can have one or more interventions. All reported interventions were evaluated and classified into the following therapeutic groups: cytotoxic therapy, targeted therapy, genetic therapy, radiotherapy, surgery and other. The trials were classified according to the reported experimental intervention types.

Systemic treatments were categorized based on the resources available on the following databases: www.drugbank.ca, National Cancer Institute Dictionary of Cancer Terms (www.cancer.gov), pubchem.ncbi.nlm.nih.gov as well as the Scopus database, the PubMed Database, Google Scholar and also through a generic internet search (Google search engine).

If randomization was not explicitly defined, manual review of the trial entries was performed to determine randomization status.

Primary sponsors were defined as entities solely responsible for conducting and overseeing the research. Secondary sponsors were defined as entities who provide logistic, monetary or any other kind of support for trial conduct. We classified the primary and secondary sponsors into 4 categories: academic institutions, industry, US government, and collaborative groups. To detect sources of monetary support, we used an algorithm based on Califf [28] as described previously [26,29]. Additionally, the geographical location of the headquarters of the primary sponsors was identified.

3. Results

The majority of trials was still recruiting at the time of the analysis (n = 38, 42%) or had not closed follow-up (n = 22, 24%). Twenty-three trials (25%) were completed, but without published results on primary endpoint.

Most trials had a single arm design, were in phase I, were non-randomized, and open label (Table 1). Five trials were phase III. The median expected enrolment was 47 (range: 6–1000).

Most of the trials had one sponsor (n = 54, 59%). Twenty-five (27%) trials were supported by one collaborator, 9 (10%) by two collaborators and 4 (4%) by three or more collaborators. Academic centres were recorded as primary sponsors in most trials (56%), followed by industry (21%).

Forty-eight trials (53%) reported only one recruitment centre. Sixteen (17%) reported 2–10 centres and 22 (24%) reported more than 10 recruitment centres. 5 (5%) trials did not report data on recruitment centres.

Database entries are regularly updated. Fifty-one trials (56%) had their last update during 2017, 27 (30%) during 2016 and 6 (6%) during 2015. Only 7 (8%) of all trials had the last entry update before 2015. Seventy-seven (85%) trials reported start and planned end date. The median expected trial duration was four years (Range: 1–20 years).

The number of analysed trials started in the period from 2005 to 2014 was stable, this increased in 2015 (Fig. 2.). ClinicalTrials.gov defines study start date as the estimated date at which the clinical study was opened for recruitment of participants, or the actual date at which the first participant was enrolled.

More than half of the registered trials were initiated in the United States (n = 51, 56%), followed by Italy (n = 8, 9%). Three (3%) trials had submitted results at the time of analysis.

Most studies investigated targeted (n = 42) or cytotoxic therapies (n = 39). One study investigated cytoreductive surgery and HIPEC with cisplatin/pemetrexed. Another trial investigated intracavitary cisplatin-fibrin. Ten studies investigated different genetic therapies. In 67% of the trials (n = 61) targeted and/or cytotoxic therapies were involved. An overview of investigated agents is provided in Table 2. Treatments involving surgery were investigated in 12 trials (13%), radiotherapy in 10 trials (11%) (Fig. 3.).

Only five studies (6%) were phase 3 studies, one was a phase 2/3 study. Four of these five investigated targeted therapies (e.g., pembrolizumab, nintedanib, ipilimumab), while one trial investigated prophylactic radiotherapy of operative tracts (Table 3).

4. Discussion

It seems that MPM research suffers from the same issues as other oncological diseases. Most trials are small, single institutional and early phase [30]. As the average cost of the drug to market process exceeds 2.5 billion dollars [31], enthusiasm about a future explosion of sponsored trials would be misguided in this relatively rare disease.

4.1. State of the art

Maximal surgical cytoreduction remains controversial and may be attempted either as non-lung-sparing surgery (EPP) or as lung-sparing surgery with extended parietal and visceral pleurectomy (extended P/D), parietal and visceral pleurectomy (P/D) or partial pleurectomy [10]. The MARS-trial assessed whether patients treated with induction chemotherapy would accept randomization to EPP or no surgery. The authors concluded that due to the observed high rate of surgical mortality, EPP was not beneficial when compared with chemotherapy treatment alone. However, these results are discussed controversially because survival was not the primary endpoint of the study, the sample size was small, and the surgical mortality was higher than expected [32,33]. As a result of this and other observational studies suggesting similarly poor outcomes, EPP has been largely abandoned in favour of less radical procedures [34].

The ASCO guidelines recommend that lung-sparing options should be the first choice and EPP may be offered only in highly selected patients in centres of excellence, while the British Thoracic Society (BTS) guidelines, state that EPP, as part of a trimodality therapy (TMT) cannot