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New Drugs

Malignant pleural mesothelioma: New hope in the horizon with novel therapeutic strategies

J. Remon [a,*], N. Reguart [b,1], J. Corral [c,2], P. Lianes [a,3]

[a] Hospital de Mataró, Barcelona, Spain
[b] Hospital Clínic, Barcelona, Spain
[c] Hospital Universitario Vírgen del Rocío, Sevilla, Spain

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ABSTRACT

Malignant pleural mesothelioma (MPM) is a rare but aggressive malignancy of the pleura, with a strong causal link to asbestos exposure. MPM incidence has been increasing in recent years and it is not expected to fall off in the next two decades. Prognosis of MPM patients is modest since the vast majority of patients are diagnosed at advanced stage and because platinum-based chemotherapy remains the cornerstone of treatment, with no standard second line treatment. Most current efforts to improve outcomes are based on a better understanding of the stromal compartment and deregulated pathways leading ultimately to the design of clinical trials based on novel therapeutic approaches such as immunotherapy or molecular-directed compounds. This review seeks to update the last clinical trials investigating novel agents in unresectable MPM.

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Introduction

Malignant mesothelioma (MM) is a rare but aggressive form of cancer arising from the mesothelial cells of the pleura (80% of all mesotheliomas originate in the pleura), peritoneum or pericardium, which has a strong causal link to asbestos exposure. Although some reports suggest a correlation between time of asbestos exposure and the risk of developing MM, data from five large studies published over the last decade provide evidence that the risk of MM is not appreciably modified by longer exposures time. Therefore, stopping asbestos contact does not subsequently modify the risk of developing MM [1].

The WHO estimates that at least 125 million people globally are exposed to asbestos in the workplace. MPM incidence is variable within and between countries because of differences in asbestos consumption [2]. Based on the International Agency for Research on Cancer (IARC), among 120,544 new cases of MM were reported during the period 1988-2002, there was a geographic distribution with 58% of these cases from North American region, 33% from European region, 5% from Oceania region, and 3% from Asian region [3]. However, global magnitude of MM is likely to be underestimated by unreported cases in mortality registries of developing countries [4], and inaccurate death certification [5]. All of these factors could explain the discrepancy in age-standardized mesothelioma incidence worldwide (Table 1) [6].

Although, the use of asbestos has already been prohibited in 55 countries worldwide, it is unlikely we see an impact on the incidence of asbestos-related diseases due to the long latency period of MM. Therefore, MPM incidence has continued rising worldwide [2], and it is not expected to drop until sometime between 2015 and 2030 [7]. Based on the World Health Organization (WHO) mortality database (1994–2008), the worldwide age-adjusted mortality rate (AAMR) for mesothelioma was 4.9 per million, increasing significantly at annual rate of 5.4%. Moreover, analysis of trends by country revealed a significant annual increase in Japan (3.5%) and a decrease in the United States (0.84%) [8], suggesting that disease burden is slowly shifting toward those countries that used asbestos more recently.

* Corresponding author at: Medical Oncology Department, Hospital de Mataró, Carretera de la Cirera, s/n, 08304 Mataró, Barcelona, Spain. Tel.: +34 937 417 700; fax: +34 937 417 780.
E-mail addresses: jremon@csdm.cat (J. Remon), nreguart@clinic.ub.es (N. Reguart), jesuscorraljaime@hotmail.com (J. Corral), plianes@csdm.cat (P. Lianes).
[1] Address: Medical Oncology Department, Hospital Clinic de Barcelona, Villarroel 170, 08036 Barcelona, Spain. Tel.: +34 932 275 400; fax: +34 934 546 500.
[2] Address: Medical Oncology Department, Instituto de Biomedicina de Sevilla-IBIS, Hospital Universitario Virgen del Rocío, Avda. Manuel Siurot, s/n, 41013 Seville, Spain. Tel.: +34 955 012 000; fax: +34 954 232 992.
[3] Address: Medical Oncology Department, Hospital de Mataró, Carretera de la Cirera, s/n, 08304 Mataró, Barcelona, Spain. Tel.: +34 937 417 700; fax: +34 937 417 780.

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MPM is a less common disease in women (with a male to female ratio of 3.8:1) [3], and has a much favourable outcome (5y-OS: 13.4% *vs*. 4.5, $p < 0.0001$) independent of confounders such as age, stage and treatment [9].

The majority of MPM patients present with unresectable disease or deemed inoperable due to age or medical comorbidities and are primarily treated with systemic therapies with the goals of improve quality of life and survival prolongation. However, MPM eventually becomes resistant to initial therapy and therefore patients have a limited life expectancy [10].

Based on the increasing incidence and the dismal prognosis, new therapeutic approaches are long awaited in MPM. This review seeks to update the state of the art for advanced MPM treatment as well as novel agents under clinical investigation such as cytotoxic therapies, targeted therapies and immunotherapy (Table 2 and Fig. 1).

Cytotoxic therapy: standard-of-care combination chemotherapy

Cisplatin and antifolate-based combination chemotherapy is the current standard first-line treatment for advanced and unresectable MPM patients. Two phase III trials showed that the combination of at least 6 cycles of cisplatin with an antifolate (pemetrexed or raltitrexed) conferred 3 months median overall survival (mOS) benefit over cisplatin alone (12.1 *vs*. 9.3 months or 11.4 *vs*. 8.8 months, respectively) [11,12] (Table 3). The substitution of cisplatin by carboplatin is widespread by the perception of lesser toxicity. Although carboplatin use is not supported by randomised evidence, three phase II studies reported that the combination of pemetrexed–carboplatin was also effective in MPM (time to progression 7 months and OS 14 months), without differences in outcome between age groups (<70 years *vs*. patients $\geqslant$ 70 years) and only a greater hematological toxicity was observed in the older population subgroup [13,14]. Moreover, an expanded access program (EAP) showed a slightly lower response rate (RR) for carboplatin-based therapy compared with cisplatin plus pemetrexed (26% *vs*. 21%), but 1-yOS was similar both groups (63% *vs*. 64%, respectively) [15].

Cisplatin and gemcitabine were incorporated into clinical practice following results from two phase II trials [16,17]. Evidence suggests that the activity of platinum based gemcitabine is as effective as platinum based pemetrexed [18,19], even with prolonged infusion of low-dose of gemcitabine [20]. However, given the lack of phase III evidence, the use of gemcitabine as first-line treatment is not supported.

Pemetrexed continuation maintenance therapy in patients who did not progress during four cycles of pemetrexed–cisplatin therapy significantly increases progression free survival (PFS) and OS over placebo in patients with advanced non-small cell lung cancer (NSCLC) [21]. Although a small Dutch study has demonstrated the safety and feasibility of continuing single agent pemetrexed after 6 courses of pemetrexed-containing regimen in MPM [22], the maintenance strategy has not yet been validated in a prospective randomized clinical trial. The ongoing randomized phase II CALGB 30901 trial is trying actually to validate this hypothesis (NCT 01085630), consequently, maintenance treatment is not standard of care.

Moreover, in MPM there is no widely approved salvage therapy beyond antifolates treatment. In the phase III pemetrexed/cisplatin trial, the use of post-study chemotherapy was analysed suggesting that second–line treatment may yield survival improvement in MPM [23]. The only randomised trial in this setting was performed before the widespread use of pemetrexed as first-line treatment, comparing pemetrexed over best supportive care (BSC). The trial showed an improvement in PFS without advantage in quality of life or OS, probably as a consequence of crossover in the BSC arm [24]. Data from the EAP also suggests that pemetrexed alone or in combination with cisplatin could be feasible as second-line treatment in pemetrexed-naïve patients [25,26]. Moreover, pemetrexed retreatment is a feasible option in fit patients, especially among those patients with longer elapsing time (>12 months) from the end of first line pemetrexed treatment until the start of second line therapy [27,28].

Despite it looks like an old standard, an exploratory analysis from the MS01 trial reported a survival advantage that approached significance with BSC plus vinorelbine *vs*. BSC alone (HR 0.80, 95% CI: 0.63–1.02, $p = 0.08$), suggesting clinical activity with this drug [29]. Then, vinorelbine appears to be a reasonable palliative option mainly in patients with ECOG PS 0 and with prolonged PFS after pemetrexed therapy [30]. *In vitro*, data suggests that vinorelbine requires BRCA1 (thought to be absent in 38% of mesothelioma samples) in order to induce apoptosis in mesothelioma [31]. A phase II trial (NCT02139904) is trying to validate the efficacy of oral vinorelbine efficacy over placebo by measuring levels of BRCA1 expression as a putative predictor of sensitivity. Likewise, in this setting, phase I clinical trials may be a reasonable option for fit patients without any treatment option [32].

Probably cytotoxic therapies have reached a plateau in MPM and new approaches based on deregulated pathways and targeted therapies are necessary to improve survival in MPM.

Table 1
Age-standardised world (ASR-W) mesothelioma incidence per 100,000. The table includes the upper and the lower incidence by gender and continent.

	ASR-W male	ASR-W female
Africa	0.1–0.4	0.3
America, Central and South	0.0–1.2	0.0–0.8
America, North	0.1–2.7	0.1–0.5
Asia	0.1–1.1	0.0–0.8
Europe	0.2–4.0	0.1–1.0
Oceania	0.1–4.7	0.6–0.6

Created by information from Cancer incidence in Five continents, volume X.

Targeted therapies

Further comprehension of molecular pathogenesis in MPM is required for developing new diagnostic tools and new-targeted therapies such as druggable mutations in NSCLC. However, MPM is being molecularly characterised mostly by the loss of tumor suppressors genes, rather than gain of function mutations. A series of 123 advanced MPM tissue samples (96 epihelioid, 22 biphasics, 5 sarcomatous histologic subtypes) were retrospectively analysed through Next-Generation Sequencing (NGS) to explore the genomic profiling. The most frequent mutated gens were *BAP1*, *APC*, *FLT3*, *TP53*, *KDR*, *KIT*, *PIK3CA*, and accumulation of mutations in several key pathways was significantly associated with an increased risk of disease progression [33]. In a recent report, none of 63 MPM samples examined showed overexpression or translocation of Anaplastic Lymphoma Kinase (ALK), excluding this gene as a possible biomarker applicable to MPM [34]. Therefore, NGS might provide a good opportunity for elucidating the molecular landscape of MPM and to identify deregulated pathways for customized therapy. The improvement of treatment selection on basis of individual characteristics and biomarkers represents a relevant challenge in the treatment of MPM.

BAP1 mutation

Because only a small fraction of asbestos-exposed individuals develop MPM, and because mesothelioma clustering is observed

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