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Editorial
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Maintenance Treatment in Malignant Pleural Mesothelioma

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Editorial

Malignant mesothelioma is a rare growth of mesothelial cells strongly associated with asbestos exposure. Mesothelial cells form the lining layers of the viscera. Mesothelioma can occur at any mesothelial layer such as the peritoneum or pericardium. The pleural layer is by far the most affected, giving rise to malignant pleural mesothelioma. This activity reviews and highlights the role of maintenance therapy in malignant mesothelioma

Mesothelioma is a rare cancer estimated to occur in approximately 2500 people in the united states every year, malignant pleural mesothelioma most common type in 81%, other sites like peritoneum 8%, pericardium and tunica vaginalis testis, median overall survival is approximately 1 year in patients with malignant pleural mesothelioma and 5 year survival is about 10%. It occurs mainly in older men median age 72 years who have been exposed to asbestos, although it occurs decades after exposure. The incidence is decreasing because asbestos use has decreased in USA, the incidence increasing in other countries as Russia, Western Europe, China and India [1].

In Egypt the new cases of mesothelioma in 2020 was 337 cases with 0.25% and number of mortalities was 307 [2]. There is no curative treatment for MPM. Systemic treatment options include chemotherapy, targeted therapy and radiotherapy, delivered separately or as part of multimodality treatment. Surgery is controversial and limited to patients with early-stage disease and good functional status. Palliative care and symptom management are essential, and the control of pleural effusions is an important factor. Several novel therapeutic agents are under investigation and may provide further treatment options for MPM in the future [3].

Most combination chemotherapy regimens that have been studied for MPM are anthracycline- and/or platinum-based. These regimens generally produce response rates of 20% or less, and median survival remains in the range of 6–12 months. In addition to these regimens, several newer agents have been tested in combination regimens, with variable results [4].

VEGF plays a key role in MPM by promoting angiogenesis and stimulating tumour growth. Recently, bevacizumab, an anti-VEGF monoclonal antibody, has been shown to be effective in MPM. The multicenter, phase III MAPS trial randomized 448 participants with MPM to receive cisplatin and pemetrexed chemotherapy with or without bevacizumab. Patients who received bevacizumab had significantly longer median (95% CI) overall survival at 18.8 (15.9–22.6) months compared with 16.1 (14.0–17.9) months in the chemotherapy alone arm (p=0.017). Patients given bevacizumab alongside chemotherapy also showed longer PFS of 9.2 (8.5–10.5) months *versus* 7.3 (6.7–8.0) months in those receiving standard care (p<0.0001) [5].

Unlike in other solid tumors like lung cancer, there is no current evidence for maintenance chemotherapy in MPM. Maintenance pemetrexed is feasible, but studies showing a better PFS, or survival benefit are lacking. Single center experience with maintenance pemetrexed without progression on carboplatin-pemetrexed induction or pemetrexed monotherapy have been described. In a cohort of 13 patients (out of 30 patients who started with platinum-pemetrexed), patients were treated with pemetrexed maintenance therapy (PMT). The median survival in the maintenance group was 8.5 *vs.* 3.4 months in the cohort without maintenance therapy. Grade 3 toxicity consisted of neutropenia, leucopenia and anemia. The only non-hematological grade 3 toxicity during PMT was fatigue (15%). The reason to stop PMT was disease progression (69%), toxicity (23%) and in patient's best interest (8%) [6].

The previous mentioned studies with cisplatin-pemetrexed with bevacizumab and nintedanib provide the first evidence for maintenance therapy with an anti-VEGF agent. In both studies maintenance anti-VEGF therapy was continued until disease progression after the initial 4–6 cycles of cisplatin-pemetrexed

+ anti-VEGF. Other drugs after chemotherapy, like thalidomide (a well-known antiangiogenic agent), were tested in a large phase III study, randomizing patients to thalidomide or BSC. Unfortunately, no improvement was observed in progression free survival (3.6 months' active agent arm *vs.* 3 in the BSC arm) [7].

To determine the benefit of maintenance pemetrexed in MPM patients in patients without progression after first line platinum-pemetrexed doublet therapy, a randomized phase II study was designed (arm 1: pemetrexed, arm 2: BSC), with progression free survival as primary outcome. (NCT01085630). The study opened in April 2010, but no results have been presented yet. Based on the advance of switch maintenance therapy in i.e., NSCLC and the previous activity of gemcitabine in phase II studies, a multi-center phase II study (NVALT 19) in The Netherlands is investigating switch maintenance therapy with gemcitabine in MPM patients without progression after platinum-pemetrexed doublet therapy and is currently open for randomization. Patients are 1:1 randomized to receive maintenance gemcitabine or BSC. The primary outcome is PFS, and secondary outcomes are i.e., toxicity and OS. The first results are expected early 2019 [8]. Another phase II randomized trial called GEMO trial designated by M.E. Sobeih that evaluates the role of maintenance gemcitabine versus BSC after induction platinum-based therapy is active and waiting for the results to be published soon. So, the role of maintenance therapy in MPM is promising and needs more investigation.

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