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Anti-programmed cell death 1 antibody zimberelimab combined with chemotherapy as the first-line treatment of advanced malignant peritoneal mesothelioma: A case report and review of literature

Immunochemotherapy for inoperable MPeM

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Abstract

BACKGROUND

Malignant peritoneal mesothelioma (MPeM) is a rare cancer with a poor prognosis at advanced stage, and the standard first-line treatment for inoperable patients is chemotherapy. Although combining programmed cell death 1 (PD-1) inhibitors with chemotherapy is generally considered safe and effective in several malignant solid tumors, there are few reports regarding initial immunochemotherapy in advanced MPeM.

CASE SUMMARY

Here, to our knowledge, we present the first case of a patient with epithelioid subtype MPeM, who was treatment-naïve and benefited from initial PD-1 inhibitor plus standard chemotherapy with a prolonged progression-free survival (PFS) and good tolerance. A 49-year-old man was admitted to our hospital for a persistent burning sensation in the abdomen. Computed tomography revealed a solid mass in the lower abdomen, which was subsequently diagnosed histologically as epithelioid subtype MPeM by core needle biopsy. The patient received eight cycles of pemetrexed 800 mg (day 1), cisplatin 60/50 mg (day 1–2), and zimberelimab (PD-1 inhibitor) 240 mg (day 1) every 3 wk. He achieved significant reduction of peritoneal tumors with remarkable improvement in symptoms. The best tumor response was partial remission with a final PFS of 7 mo. No immune-related adverse event occurred during the combination treatment.

CONCLUSION

The outcome of the present case demonstrates the promising anti-tumor activity of immunochemotherapy to treat inoperable MPeM in the future.

Key Words: Malignant peritoneal mesothelioma (MPeM); Immune checkpoint inhibitors; Immunotherapy; Zimberelimab; Chemotherapy; Case report

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Core Tip: Malignant peritoneal mesothelioma (MPeM) is a rare cancer with a poor prognosis at advanced stage. Here, we present the first case of a patient with epithelioid subtype MPeM, who was treatment-naïve and benefited from initial PD-1 inhibitor plus standard chemotherapy with a prolonged progression-free survival (PFS) and good tolerance. We would like to share our experience with immunochemotherapy, which will help clinicians make appropriate decisions in the future.

INTRODUCTION

Malignant peritoneal mesothelioma (MPeM) is a lethal and highly aggressive tumor that originates from peritoneal mesothelial cells. It has an extremely low incidence rate of approximately 0.13 cases per 100,000 individuals and accounts for 15%–20% of malignant mesotheliomas[1,2]. MPeM is histologically classified into three subtypes: epithelioid, biphasic, and sarcomatoid. The epithelioid subtype constitutes 70%–80% of all MPeM cases and is associated with less aggressive biological behavior than the others[3]. Typical symptoms of MPeM include abdominal discomfort, distention, and ascites[4]. However, the symptoms are nonspecific, leading to most patients being diagnosed at an advanced stage that is unsuitable for surgery. The median overall survival (OS) for untreated MPeM patients is reportedly <12 mo[5].

Currently, cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) remains the primary standard therapy for operable MPeM. However, combination chemotherapy is the preferred treatment strategy for inoperable disease, with an approximate objective response rate (ORR) of 38% and a poor median OS of 15.4 months[6]. Therefore, innovative approaches are urgently needed for the treatment of inoperable MPeM to improve tumor response and survival outcomes.

Malignant pleural mesothelioma (MPM) and MPeM have the same pathological origin. In recent years, several encouraging reports have shown that MPM shows great tumor response to immune checkpoint inhibitors (ICIs)[7-10]. However, thus far, few clinical studies have focused on the efficacy and safety of the first-line ICI therapy in advanced MPeM regardless of monotherapy or immunochemotherapy. We herein report a case of 49-year-old man with MPeM who was treated with cisplatin, pemetrexed, and zimberelimab (a novel, fully humanized anti-programmed cell death 1 [PD-1] antibody granted firstly in China); he achieved progression-free survival (PFS) of 7 mo with good tolerance.

CASE PRESENTATION

Chief complaints

A 49-year-old man was referred to our hospital in December 2021 with an abdominal mass that had persisted for over three weeks.

History of present illness

The patient initially presented with a burning sensation in the abdomen and a sudden weight loss of 10 kg between November and December 2021. The abdominal mass was observed by imaging scan, and thus, he was referred to our hospital for diagnosis and treatment as the severity of his clinical symptoms progressively increased during the course of the illness.

History of past illness

He had a history of untreated hepatitis B for more than 30 years.

Personal and family history

He had no previous personal or family history.

Physical examination

The Eastern Cooperative Oncology Group-performance status (ECOG-PS) score was 0, and his vital signs remained stable. Except his symptoms, no remarkable signs were observed.

Laboratory examinations

Immunohistochemical analysis revealed that the cells were positive for calretinin (Figure 1), Wilm's tumor gene 1, D2-40, and cytokeratin 5/6, weakly positive for desmin, and negative for SMA, Dog-1, Bcl-2, HMB45, Melan-A, and CD99.

Imaging examinations

Abdominal computed tomography (CT) revealed a solid mass in the abdomen (8.9×5.2 cm) with multiple lesions in the omentum and abdominal cavity, as well as a cystic mass in the lower abdomen (Figure 2A).

FINAL DIAGNOSIS

The patient was pathologically diagnosed as stage III MPeM (cT3N0M1) by core needle biopsy[11].

TREATMENT

As the disease was in advanced stages and thus ineligible for CRS, with the consent and decision of the patient and his family, he was given pemetrexed 800 mg (day 1), cisplatin 60 mg (day 1-2), and zimberelimab 240 mg (day 1), every 3 wk for four cycles from January to March 2022. However, due to the moderate increase in serum creatinine to 116.6 $\mu\text{mol/L}$ (normal range in male: 53–106 $\mu\text{mol/L}$) caused by the chemotherapeutic agents, cisplatin was reduced to 50 mg fifth cycle onward. Subsequently, the patient received three additional cycles of this combination regimen.

OUTCOME AND FOLLOW-UP

In April 2022, after five treatment cycles, the maximum lesion had shrunk remarkably from 8.9×5.2 cm to 4.1×4.0 cm (Figure 2B), and the levels of CA125, which is a tumor marker for MPeM, decreased from 64.1 U/mL to 15.1 U/mL over this period. According to Immune-based Response Evaluation Criteria in Solid Tumors (iRECIST), the efficacy was evaluated as partial response. However, in July 2022, CT imaging showed that the target lesion had increased from 4.1×4.0 cm to 4.4×4.0 cm (Figure 2C), and a new irregular solid mass was observed in the pelvic vesicorectal fossa area, suggesting progressive disease (Figure 2D). At his last follow-up in September 2022, he was finally identified as having progressive disease with a PFS of 7 mo. Consequently, he discontinued the combination regimens and was transferred to a local hospital where he was subsequently lost to follow-up. He did not experience any significant immune-related adverse event.

DISCUSSION

While the cancer is still in an operable stage, CRS and HIPEC have been extensively studied and recommended as the cornerstone of therapeutic strategy for MPeM because of their acceptable long-term survival rates[1]. However, for patients who are ineligible for or unwilling to undergo surgery, cisplatin plus pemetrexed has remained the standard first-line treatment for almost two decades in MPM; according to a phase III study, it offers a limited median PFS and OS of 5.7 mo and 13.2 mo, respectively[12]. Owing to the similarity between MPM and MPeM, cisplatin plus pemetrexed is also recommended as the standard therapy for MPeM according to the current guidelines[13]. Therefore, novel therapies are urgently needed for the treatment of MPeM.

In recent years, PD-1/PD-L1 inhibitors have emerged as a prominent avenue in tumor treatment and have been used in the treatment of various malignancies. Multiple PD-1/L1 and CTLA-4 inhibitors have shown good clinical efficacy and safety in several studies, providing promising treatment options for MPM patients[14]. However, there

is currently limited evidence regarding the clinical value of PD-1/L1 inhibitors in MPeM.

NIBIT-MESO-1 was the first study to demonstrate encouraging efficacy of PD-1/L1 inhibitors in patients with unresectable malignant pleural or peritoneal mesothelioma who received combination immunotherapy with tremelimumab (a CTLA-4 inhibitor) and durvalumab (a PD-L1 inhibitor). Among the 40 patients enrolled, 28% (11/40) achieved an immune-related objective response, but only two were MPeM patients[15].

¹ The PROMISE-meso trial was the first randomized controlled study to evaluate the efficacy of anti-PD-1 therapy in pre-treated patients with relapsed MPM. In this multicenter phase III study, 144 patients were randomly assigned (ratio 1:1) to receive either pembrolizumab or single-agent chemotherapy. The objective response rates were 22% and 6%, respectively[16]. After the PROMISE-meso study, CONFIRM is the first

⁹ multicenter, placebo-controlled, double-blind, randomized phase III clinical trial to evaluate the efficacy of the PD-1 inhibitor nivolumab in ⁴ patients with either pleural or peritoneal mesothelioma that had progressed after platinum-based chemotherapy. ⁸ A total of 332 participants (only 16 MPeM patients) were enrolled; the mPFS was 3.0 mo (95%CI: 2.8–4.1 months) and 1.8 mo (95%CI: 1.4–2.6 months) in the nivolumab group (n

= 221) and the placebo group (n = 111), respectively; meanwhile, the mOS was 10.2 mo (95%CI: 8.5–12.1 months) and 6.9 mo (95%CI: 5.0–8.0 months), respectively. The results showed that nivolumab was superior to the placebo in terms of both mPFS and mOS[9].

A phase II trial, which investigated the effect of atezolizumab (a PD-L1 inhibitor) in 20 advanced MPeM patients previously treated with platinum-pemetrexed chemotherapy, showed promising anti-tumor activity against MPeM, with an ORR of 40%, 1-year PFS rate of 61%, and 1-year OS rate of 85%⁶[4]. ¹ The JAVELIN study was a single-arm

prospective clinical trial that evaluated the efficacy and toxicity profile of avelumab (a PD-L1 inhibitor) in 53 patients with predominantly pleural and peritoneal mesothelioma[17], and it reported a low ORR of approximately 10%. CheckMate 743

² was a phase III clinical trial that compared the efficacy and safety of nivolumab + ipilimumab and chemotherapy as the first-line treatment for unresectable MPeM. The

reported mOS was 18.1 and 14.1 mo, respectively, and the 3-year OS rates were 23% and 15%, respectively, supporting that the combination of immunotherapy had superior outcomes. Additionally, clinical benefit with nivolumab + ipilimumab was also observed across all subgroups regardless of PD-L1 expression and its clinical efficacy was particularly favorable in epithelioid subtype MPeM[18].

Cerbone *et al* reported a case of a heavily treated patient with MPM who underwent multiple anticancer treatments, including chemotherapy and ICIs, and achieved a PFS of >26 mo after the administration of nivolumab[19]. Furthermore, several clinical trials have explored the safety and efficacy of immunotherapies targeting the PD-1 or PD-L1 pathway as first-line or subsequent treatments for patients with MPM[10,16,20-23]. Although these studies only provided preliminary results, the ORR ranged from 10%–30%. This suggests that a small subset of patients may benefit from PD-1/PD-L1 monotherapy, and more effective combination therapies should be explored to improve antitumor efficacy. Notably, some studies showed that PD-L1 expression is not significantly associated with ORR[24,25].

Thus far, few prospective clinical studies have investigated the efficacy of ICIs in combination with chemotherapy for advanced MPeM. Durvalumab, an anti-PD-L1 antibody, in combination with cisplatin and pemetrexed has demonstrated sufficient efficacy, safety, and tolerability in two phase II studies for the first-line treatment of unresectable MPM[26,27]. Additionally, several case reports have upheld the efficacy of this combination therapy. Foote *et al* reported on two patients who received pembrolizumab in addition to platinum and pemetrexed treatment, and both achieved a durable partial response. Notably, neither of the two patients had established biomarkers for ICI therapy, such as tumor mutational burden and PD-L1 expression[28]. Huang *et al* also reported a similar case with a short survival duration of 2 mo[29]. Thus, we hypothesize that ICIs and chemotherapy have synergistic activities in MPeM, and initial immunochemotherapy may be feasible as an optional first-line regimen. Notably, PD-L1 expression is observed in nearly 50% of MPeM patients but only in 30% of MPM patients[30].

Zimberelimab is a novel, fully humanized anti-PD-1 monoclonal immunoglobulin G4 (IgG4) developed from the OmniRat transgenic platform[31-34]. Compared with another PD-1 inhibitor (pembrolizumab, not a head-to-head comparison) in a phase II study, zimberelimab achieved a higher ORR in relapsed/refractory classical Hodgkin lymphoma[35,36]. We attempted to adopt platinum-based chemotherapy + zimberelimab for our relatively younger patient. The present case finally achieved rapid tumor response and an acceptable PFS of 7 mo.

To our knowledge, this is the first report of initial immunochemotherapy with a PD-1 inhibitor and chemotherapy being used as the first-line regimen for MPeM, and it achieved a favorable PFS. However, a limitation of this case is that PD-L1 expression was not tested because it is not a routine recommendation according to current guidelines.

CONCLUSION

In the present case of inoperable MPeM, initial combination therapy with a PD-1 inhibitor and chemotherapy achieved anti-tumor activity, which can be considered for personalized therapy of such a rare cancer. We also recommend that a well-designed prospective clinical trial could be conducted to explore the potential benefit of immunochemotherapy as a new first-line treatment option for MPeM.

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