

Life-Threatening Hepatitis with Cholangitis as a Side Effect of Dual Immunotherapy in the Treatment of Malignant Pleural Mesothelioma

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ABSTRACT

Abbreviations: OS: Overall Survival; MPM: Malignant Pleural Mesothelioma; WHO: World Health Organization; FDA: Food and Drug Administration; EMA: European Medicines Agency

Introduction

Malignant pleural mesothelioma (MPM) is a rare and aggressive neoplasm originating from the mesothelial lining of the pleural cavity [1,2]. Its annual incidence is increasing globally and is closely associated with asbestos exposure (accounting for 80% of cases), with a long latency of almost 40 years between exposure and disease onset. The prognosis of MPM is poor, with a median survival of less than 14 months and a 5-year survival rate of less than 10%. In Europe, due to differences in asbestos exposure, MM is more common in men (1.7/1000) than in women (0.4/1000). The median age at diagnosis is 70 years in Western countries. According to the 2021 World Health Organization (WHO) classification, MPM is categorized into three

main histological subtypes: epithelioid (50–70% of cases), characterized by a better prognosis, sarcomatoid (10–20% of cases), more aggressive and typically resistant to chemotherapy, and biphasic, with features of both [3-5]. Platinum and pemetrexed chemotherapy has been the standard of care for unresectable disease since 2004, and no other treatment is approved in the second- and third-line settings [2,6]. However, immunotherapy has improved survival outcomes for patients with a wide range of cancers, including mesothelioma. The combination of ipilimumab and nivolumab was approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) based on the results of the randomized phase III CheckMate 743 trial [7].

In this study, nivolumab plus ipilimumab significantly improved overall survival (OS) compared with platinum and pemetrexed chemotherapy in unresectable patients with MPM who had not received chemotherapy. Three-year efficacy and safety updates showed, after a minimum follow-up of 35.5 months, that immunotherapy with ipilimumab plus nivolumab continued to provide an OS benefit over chemotherapy (HR 0.75) and 28% of patients had a sustained response after 3 years in the immunotherapy arm [8]. As a second-line treatment, nivolumab achieved a statistically significant improvement in PFS and OS compared with placebo in previously treated MM patients in the randomized phase III CONFIRM trial [9]. Several ongoing phase III trials should provide robust evidence of the benefits of combining immunotherapy with chemotherapy in the first-line treatment of MPM [2]. Despite all the recent results, it is still unclear which patients with mesothelioma benefit from immunotherapy and which do not. In the Checkmate-743 trial, 28% of patients who responded to the ipilimumab-nivolumab combination continued to respond after 36 months. On the other hand, 18% of patients treated with immunotherapy became primary refractory compared with 5% of patients treated with chemotherapy. The occurrence of early progression or even hyperprogressive disease in patients with MPM treated with immunotherapy has also been reported in other studies [10].

The combination of ipilimumab and nivolumab in first-line treatment mainly benefits non-epithelioid patients, partly because chemotherapy is ineffective for this histological subtype, while the same level of benefit is not observed in epithelioid patients. In second- and third-line therapy, PD-1 inhibitors as monotherapy were superior to placebo in terms of OS and PFS in the CONFIRM trial, but were not superior to chemotherapy (vinorelbine or gemcitabine) in the PROMISE-meso trial [9,11]. Both CONFIRM and PROMISE-meso trials reported responses with immunotherapy in epithelioid patients. In the PROMISE-meso trial, the ORR was 22% in epithelioid patients treated with pembrolizumab compared with 6% in patients treated with chemotherapy. Given these inconsistent results and the discrepancies with the use of immunotherapy in the treatment of mesothelioma, it is crucial to identify predictive biomarkers, especially for epithelioid patients who will benefit from immunotherapy. Several attempts are underway to identify predictive biomarkers of response to immunotherapy. Unlike other cancers, the predictive value of PD-L1 and TMB for response to immunotherapy in patients with MM is still weak and uncertain. This is likely due to the extensive tumor genomic heterogeneity among patients and the histological differences typical of mesothelioma [11,12]. Genomic research and the TIME study are testing several new potential predictive biomarkers.

Incorporating genomic approaches that can detect structural variants and transcriptomics to assess antigen processing and presentation could improve patient selection for immunotherapy. In an exploratory analysis of the Checkmate-743 trial, expression of CD8A, STAT1, LAG3, and CD274 (PD-L1) was quantified using RNA sequenc-

ing. A high score of four inflammatory response genes was associated with improved OS in the nivolumab plus ipilimumab group (mOS 21.8 months vs. 16.8 months in patients with a low score), suggesting its potential positive predictive role. These data require prospective validation. Cancer-associated fibroblasts, T cells, TAMs, and MDSCs have an immunosuppressive role in mesothelioma [13]. Mannarino and colleagues showed that patients with epithelioid MM with long OS (>36 months) were characterized by an inflammatory background with higher B-cell expression (CD20+) and a prevalence of TLS formation compared with patients with epithelioid MPM with short OS (<12 months), which showed a higher frequency of neutrophils and M2 macrophages ($p = 0.025$). TLS have been identified in various types of cancer and are associated with a better response to immunotherapy. Immunotherapy appears to promote the formation and activity of TLS, and this may explain the possible role of TLS and B-cell infiltration as a positive predictive biomarker of response to immunotherapy in various types of cancer [14,15].

Other immune checkpoint molecules besides PD-1/PD-L1, notably LAG-3, TIM-3, and VISTA, represent novel biomarkers of interest. In particular, VISTA is expressed on the surface of myeloid cells, particularly on TAMs, and is a negative checkpoint regulator that inhibits T cell proliferation and activation. Interestingly, pleural mesothelioma shows the highest levels of VISTA expression among all cancers studied, particularly in the epithelioid subset. Therefore, VISTA is being investigated as a potential predictive biomarker of response to immunotherapy in mesothelioma and could become one of the potential targets for overcoming immunotherapy resistance and a molecular target for improving immune regulation [16]. Despite therapeutic advances in mesothelioma, our knowledge of the factors that underpin immunotherapy response is limited. The genomic heterogeneity of patients and the histological diversity of mesothelioma underscore the need for biomarkers that will indicate which patients will benefit from immunotherapy. Understanding the mechanisms associated with primary and secondary resistance to immunotherapy will further improve treatment outcomes for patients with mesothelioma.

Case Report

The 59-year-old patient, smoker with 20 pack years, had never had lung disease before. Her father died of lung cancer. She spent her childhood in the immediate vicinity of an asbestos factory. In 1992, she was hospitalized for pancreatitis, and after recovering from it, she underwent a cholecystectomy. Since the summer of 2024, she has noticed dyspnea and faster fatigue during physical activity and walking uphill. She has also been coughing a little. She was not febrile. She complains of discomfort in the epigastrium. She has had gastritis for a long time. She lost 6-7 kg of body weight in a few months. She was examined by a pulmonologist on December 2, 2024, and then, due to an extensive left-sided pleural effusion, a thoracentesis was performed on the left side and 2000 ml of yellowish effusion was evacuated. After that, she was significantly better in terms of reduced dyspnea, and

her appetite has improved significantly. She denies coughing and has not been febrile. On December 9, 2024, 2000 ml of pleural effusion was evacuated again from the left side. On December 13, a transthoracic biopsy was performed on one of the nodular thickenings of the left pleura, verified by MSCT. The pathohistological findings of the same speak in favor of epithelioid mesothelioma. On January 8, 2025 she was seen by the multidisciplinary team for thoracic tumors and systemic oncological treatment and dual immunotherapy was recommended.

On January 14, she received the first application of nivolumab and ipilimumab. After that, she had a fever of up to 40 °C for 2 days with chills and shivering. On February 4, she received the second application of nivolumab. The day after, she had nausea. On February 14, she underwent left thoracentesis due to shortness of breath, when 1600 ml of effusion was evacuated. During the course of dual immunotherapy treatment, she developed hyperthyroidism as a side effect, and was treated with atyrazole and propranolol. She also had some itching all over her body, suggesting mild iatrogenic dermatitis. On February 25, she received a third application of nivolumab with a second application of ipilimumab. After that, she was well, she had no dyspnea or cough. From March 10, she developed pain along her legs, distal from the thighs. On March 14, she became extremely icteric. She was not febrile. She was extremely lethargic. She was mostly lying and sitting. At home, she measured extremely low blood pressure values. When she was admitted, her blood tests showed, among other things: total bilirubin 303 µmol/L, conjugated bilirubin 268 µmol/L, AST 249 U/L, ALT 392 U/L, GGT 803 U/L, LDH 462 U/L, amylase 126 U/L, lipase 131 U/L. Her other blood tests were normal. On the X-ray of the lungs, inhomogeneous infiltrations of the lung parenchyma were observed on the right, in the sense of possible pneumonitis.

She was afebrile and had normal oxygen saturation. She was hospitalized for hepatitis with cholangitis and subsequent icterus as a result of the dual immunotherapy she received. From the time of admission, methylprednisolone was started intravenously at a dose of 2 mg per kg of body weight. Shortly after admission, MSCT of the chest and abdomen was performed, which described the right lung with peribronchial consolidations that also affected the acini that confluent with each other, with accompanying GGO areas and sparing of the subpleural space, all in the sense of iatrogenic pneumonitis. In addition, regression of the pleural effusion on the left was described in comparison with the scan before immunotherapy, and local nodular thickening of the pleura now showed marked regression. Intrahepatic and extrahepatic bile ducts were not dilated. After 7 days, she was still extremely icteric with further increase in bilirubin and still high values of liver transaminases (total bilirubin 484 µmol/L, conjugated bilirubin 429 µmol/L, AST 149 U/L, ALT 428 U/L, GGT 1190 U/L, LDH 266 U/L, ALP 749 U/L). After consulting an immunologist and following current recommendations mycophenolate mofetil was added to her therapy, initially 500 mg twice a day.

After 2 weeks of the mentioned therapy, the control X-ray of the lungs shows a regressive dynamics of the infiltrate in the sense of pneumonitis. Then, in the blood results, a pathological finding of thyroid hormone (TSH 49,300 mIU/L, T4 10.8 nmol/L, fT4 <0.5 pmol/L, T3 <0.3 nmol/L, fT3 <0.6 pmol/L) was observed in terms of iatrogenic thyroiditis with consequent hypothyroidism, which is why levothyroxine was added to her therapy. After 2 weeks, we tried to gradually reduce the dose of methylprednisolone by 0.25 mg per kg of body weight, but since extremely high bilirubin values persisted with jaundice, we continued with 2 mg per kg. After three weeks of therapy, the blood tests still showed: total bilirubin 391 µmol/L, conjugated bilirubin 357 µmol/L, AST 84 U/L, ALT 194 U/L, GGT 619 U/L, LDH 210 U/L, ALP 352 U/L, AMS-s 56 U/L, lipase 65 U/L. For this reason, a gastroenterologist was consulted again. She also underwent MR cholangiopancreatography, which did not detect dilated intrahepatic bile ducts, the common hepatic duct measured up to 8 mm, and the common bile duct up to 9 mm and gradually narrowed towards the papilla. She then underwent EUS with a linear echoendoscope, which showed the main bile duct from the duodenum measuring 7 mm proximally and gradually narrowing towards the p. Vateri. No echoes were seen within the lumen or choledocholithiasis.

Since there was no clinical improvement and she was still extremely icteric with high bilirubin values, after consulting with a gastroenterologist and a nephrologist, she underwent plasmapheresis with fresh frozen plasma for 5 days. In addition, her daily dose of mycophenolate mofetil was increased to 1 g twice a day. After the plasmapheresis, there was a minimal drop in the bilirubin value, and she was still extremely icteric. In addition, she became highly febrile on two occasions every day, and in her blood tests, low leukocyte values began to be recorded, along with a regular finding of increased inflammatory reactants. Because of febrility, she underwent extensive microbiological investigation (PCR of nasopharynx, multiplex PCR of bronchoaspirate, blood culture, urine culture), but no infectious agent that could have been the cause of febrility was isolated from any sample. After leukopenia, her blood tests also showed anemia and thrombocytopenia, and a bone marrow aspiration was performed. Leukopenia was considered a possible side effect of mycophenolate mofetil, which is why it was omitted from the therapy. Over the following days, the patient's clinical condition deteriorated; despite filgrastim and backup antibiotics, the white blood cell count did not recover, she was often highly febrile and there was a marked increase in the values of inflammatory reactants, all in the sense of a septic state. On the other hand, her bilirubin values persisted at a high level. After two months of hospitalization and all applied therapeutic measures, our patient died.

Immunotherapy-induced hepatotoxicity can range from mild elevation of liver aminotransferases to rarely, fulminant liver failure [17]. The reported incidence of immunotherapy-induced hepatitis varies widely, with most clinical trials reporting a low rate around 5.8%

[18]. However, some retrospective studies report higher rates of that adverse effect, up to 64% [19]. Moreover, the management of hepatotoxicity recommended by various societies differs among professional societies, and some studies have suggested approaches that diverge from the guidelines [20]. The American Society of Clinical Oncology guidelines require close monitoring of liver tests prior to each infusion and/or weekly for patients with grade 1 hepatitis [21]. In grade 2 hepatitis, ICIs should be withheld temporarily, but may be restarted following recovery to grade 1 or less while taking prednisone ≤ 7.5 –10 mg/day. Corticosteroid therapy with prednisone 0.5–1 mg/kg/day (or equivalent) should be started. In addition, more frequent monitoring should be done in patients with no improvement after 5 days. In patients with grade 3 hepatotoxicity, ICIs should be permanently discontinued, and prednisone 1–2 mg/kg/day or methylprednisolone 1–2 mg/kg prescribed. Steroids should be tapered over a course of 4 weeks in patients with improvement of liver tests. In refractory cases, a second agent such as mycophenolate or azathioprine should be considered.

Grade 4 toxicity is managed much like grade 3, but methylprednisolone 2 mg/kg may be considered. Liver imaging and biopsy may be considered in patients with grade 3 and 4 hepatitis to assess for alternative causes. We present a patient who, after receiving three applications of nivolumab and two applications of ipilimumab for pleural mesothelioma, was hospitalized due to a marked deterioration of her general condition in the form of pronounced jaundice, due to iatrogenic hepatitis with cholangitis. In addition, she developed pneumonitis and thyroiditis as a side effect of immunotherapy. According to the clinical picture and blood tests, these were life-threatening side effects. She was treated according to the current recommendations for the treatment of immunotherapy-mediated hepatitis with additional therapeutic options after consultation with a gastroenterologist and nephrologist. In addition, she underwent extensive diagnostic work-up. Despite everything, the patient died after two months of hospital treatment. The case of this patient tells us that we must seriously consider the side effects of immunotherapy, especially if someone is on dual immunotherapy. If, as in this case, it is a rare life-threatening side effect, it also requires a multidisciplinary approach in terms of treatment and diagnostics. Unfortunately, the presented case of the patient is a rare, extremely serious and life-threatening case of a side effect of immunotherapy that ended in death.

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