RESIDENT'S CORNER

Vanishing bile duct syndrome associated with pazopanib after progression on pembrolizumab

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Pazopanib, a tyrosine kinase inhibitor, has been a standard first-line treatment for metastatic renal cell carcinoma (mRCC). Recent trials combining pazopanib with programmed cell death protein 1 (PD-1) inhibitors, including pembrolizumab, have shown excessive hepatotoxicity. We report a case of fatal hepatotoxicity from vanishing bile duct syndrome (VBDS) associated with pazopanib treatment, in a patient previously exposed to pembrolizumab. This is the first report of pazopanib-induced VBDS. We postulate whether prior exposure to pembrolizumab predisposed towards pazopanib-induction of VBDS, and discuss potential risks of sequential PD-1 inhibitor followed by pazopanib in mRCC, due to prolonged half-lives of PD-1 inhibitors.

Key Words: pazopanib, pembrolizumab, vanishing bile duct syndrome, hepatotoxicity

Introduction

Pazopanib, a vascular endothelial growth factor (VEGF) targeted tyrosine kinase inhibitor (TKI), has been a standard first-line treatment for metastatic renal cell carcinoma (mRCC). When compared to sunitinib, it has shown similar response rates (overall response rate of 31% versus 25%) and overall survival (median of 28.4 months versus 29.3 months).[1] Additionally, pazopanib is better tolerated than sunitinib, with less fatigue, hand-foot syndrome and mouth sores, and improved health-related quality of life scores; most of pazopanib's adverse effects are low grade and clinically manageable.[1,2] While mild elevations of hepatic transaminases are common, grade 3-4 elevations (> 5 times the upper limit of normal) are encountered in a small proportion of patients only, up to 12%.[2] There have only been three reports of death in the literature due to pazopanib-induced hepatotoxicity.[2,3]

Recently, immune checkpoint inhibitors targeting programmed cell death protein 1 (PD-1), its ligand (PD-L1) and cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) have demonstrated activity in mRCC.[4,5] PD-1 inhibitor, nivolumab, in combination with CTLA-4 inhibitor, ipilimumab, has demonstrated improved overall survival compared to sunitinib in first-line treatment of intermediate and poor prognosis patients as assessed by the International Metastatic Renal Cell Carcinoma Database Consortium.[4] The activity of immune checkpoint inhibitors in mRCC has led to several studies looking at the combination of checkpoint inhibitors with VEGF-targeted TKIs.[5-7] Some of these combinations, such as atezolizumab and bevacizumab, and avelumab and axitinib, have demonstrated survival advantages in the first-line setting when compared to sunitinib.[5] Unfortunately, the combination of pazopanib and PD-1 inhibitor pembrolizumab has demonstrated unacceptable hepatotoxicity.[7] In a phase I trial, Grade 3-4 alanine-aminotransferase (ALT) elevations were seen in 60%-70% of patients on combination pazopanib and pembrolizumab, but were not associated with any treatment-related deaths.[7] The combination of nivolumab and pazopanib also demonstrated significant hepatotoxicity.[6] Subsequently, further studies examining the combination of pazopanib and PD-1 inhibitors have been abandoned.[6,7]

It is anticipated that immunotherapy will increasingly be used as first-line treatment of mRCC, either as a doublet of checkpoint inhibition (e.g. ipilimumab and nivolumab) or as a combination of PD-1 inhibitors and VEGF-targeted TKIs. Currently, there is little data to

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suggest how to sequence subsequent treatments, in particular, which VEGF-targeted TKI is most suitable following prior first-line checkpoint inhibition. Better understanding potential adverse events that might result from specific sequences of first- and second-line treatments will be helpful. Here we report a case of fatal hepatotoxicity following pazopanib treatment, in a patient previously exposed to pembrolizumab.

Case report

A 70-year-old man developed metastatic recurrence of RCC 5 years after resection of his primary tumor. He was initially treated with multiple surgical resections for metachronous oligometastatic recurrences. He then received stereotactic body radiotherapy to an isolated lung metastasis followed by pembrolizumab (8 cycles of 200 mg every 3 weeks). This was ceased after five cycles of pembrolizumab due to further disease progression with a new liver metastasis (15 mm) and progressive hilar and mediastinal lymph node metastases.

The patient then commenced pazopanib 800 mg daily (P800), 1 month after his final dose of pembrolizumab. Liver function tests were normal at baseline and he had no history of liver disease. He tolerated pazopanib for 9 days before developing severe nausea, vomiting, diarrhoea and lethargy. Liver function tests remained normal. His symptoms resolved following cessation of pazopanib. Twelve days after ceasing pazopanib, he was recommenced on a reduced dose of 400 mg daily (P400). Four days later, his symptoms returned with new onset jaundice and he was admitted to hospital. His liver function tests (LFT) were markedly deranged, Figure 1, with a bilirubin of 160 µmol/L and elevated liver enzymes (ALT 820 U/L, gamma-glutamyltransferase 170 U/L, alkaline phosphatase 470 U/L). Hepatic synthetic function was initially preserved with a normal albumin and INR and there was no evidence of encephalopathy. Imaging with abdominal ultrasonography and magnetic-resonance imaging excluded biliary obstruction, Budd-Chiari syndrome, and progression of his liver metastasis. A hepatic screen excluded viral, metabolic and autoimmune etiologies. He did not consume alcohol and had no exposure to alternative or other hepatotoxic medications.

Aside from jaundice, the patient's clinical symptoms again resolved rapidly with cessation of pazopanib. However, his bilirubin continued to rise. He was commenced on ursodeoxycholic acid (URSO). Due to his previous exposure to pembrolizumab, he was also treated empirically with methylprednisolone (mP; 2 mg/kg intravenously) for 5 days, for possible late onset immune-related adverse effect hepatitis, but his liver function tests did not improve with his bilirubin remaining over 300 µmol/L, Figure 1. Given the diagnosis remained unclear, a diagnostic liver biopsy was performed. The biopsy demonstrated ductopenia, cholestasis and degenerative hepatocyte changes with mild portal and lobular inflammation. There was no evidence of interface hepatitis or cirrhosis. Cytokeratin 7 (CK7) and Cytokeratin 19 (CK19) immunohistochemistry showed only two bile ducts, despite nine portal tracts being present and an adequate sample measuring 18 mm in length. The two bile ducts present showed reactive changes with

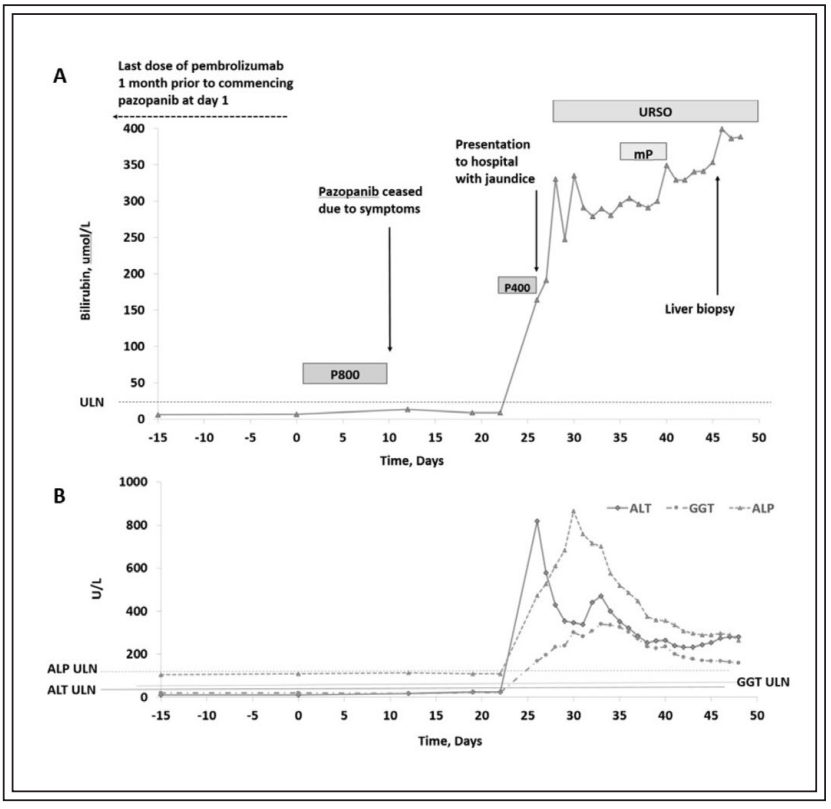

Figure 1. (A) Graph showing changes in bilirubin over time since the start of pazopanib, with a summary of systemic treatments given. **(B)** Corresponding graph showing changes in ALT, ALP and GGT over time since the start of pazopanib.

nuclear pleomorphism and loss of polarity. Overall, these findings were consistent with vanishing bile duct syndrome (VBDS). The patient's bilirubin continued to rise until a plateau of almost 400 µmol/L, 3 weeks after admission to hospital. He subsequently died of cholestatic hepatic failure 2 months after initial commencement of pazopanib and 3 months after the last dose of pembrolizumab.

Discussion

We have described a fatal case of VBDS in a patient treated with pazopanib and previously exposed to pembrolizumab. VBDS is a rare but serious condition for which there is currently no known means of prevention or treatment.[8] Diverse drug precipitants for VBDS have been reported, including one case of pembrolizumab-induced VBDS with the patient presenting 8 days after first exposure to pembrolizumab.[8,9] In this case, despite the patient's prior exposure to pembrolizumab, the clinical context suggests that the VBDS was pazopanib-induced. Unlike the previously reported case of pembrolizumab-induced VBDS, this patient's first exposure to pembrolizumab was more than 4 months prior and treatment cessation over a month prior to symptoms. Instead, he rapidly developed symptoms after commencing pazopanib, which resolved on drug interruption, then rapidly recurred on re-challenge, accompanied by liver function derangements and subsequent biopsy-proven VBDS.

This is the first reported case of biopsy-proven VBDS induced by pazopanib. There are only two other cases of pazopanib hepatotoxicity with liver-biopsies in the literature.[3] Both of these showed prominent biliary injury, but without loss of bile ducts.[3] Although the pathogenesis of VBDS is not well understood, it is thought to have an immunoallergic basis.[8] As such, prior exposure to pembrolizumab may have predisposed towards pazopanib-induction of VBDS. Another consideration is that the severe hepatotoxicity in this case may have resulted from the combination of pazopanib and pembrolizumab. Immune checkpoint inhibitors have relatively long half-lives, with pembrolizumab's terminal half-life being 26 days.[10] Given pazopanib was commenced 1 month following pembrolizumab cessation, this patient essentially received combined treatment of pembrolizumab with pazopanib, albeit with lower levels of pembrolizumab in circulation. While the severe hepatotoxicity seen in our patient parallels the phase I data showing marked hepatotoxicity from the combination of pazopanib and PD-1 inhibitor therapy,[6,7] we believe VBDS is unlikely to have been the common underlying pathology for these patients.

The treatment landscape for mRCC is changing, with immune checkpoint inhibitors likely to be increasingly used as first-line treatment, either as part of dual CTLA-4 and PD-1 checkpoint blockade, or in combination with VEGF targeted TKIs. Already, the combinations of nivolumab and ipilimumab, atezolizumab and bevacizumab, and avelumab and axitinib have shown survival advantages compared to standard of care sunitinib, as first-line therapy of mRCC.[4,5] Further trials in progress for immune checkpoint inhibitors combined with VEGF-targeted TKIs include the KEYNOTE-426 phase III trial of TKI axitinib with pembrolizumab, versus sunitinib. Taking into account the long terminal half-life of immune checkpoint inhibitors and concerns of excess hepatotoxicity from combining pazopanib with PD-1 inhibitors, caution should be taken when starting pazopanib as a further line of therapy shortly after ceasing checkpoint inhibitors.[6,7,10] Given there are many alternative treatment options for mRCC, we would be wary of using pazopanib in such situations. Likewise, although rare, VBDS should be considered in all patients with cholestatic liver function tests receiving pazopanib therapy. □

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