Hepatitis B virus reactivation following T-cell engager therapy in multiple myeloma despite negative hepatitis B core antibody serology: implications for screening in patients with hematological malignancies

Multiple myeloma (MM) is an incurable hematological malignancy caused by the clonal proliferation of plasma cells. Proteasome inhibitors, immunomodulatory agents and anti-CD38 monoclonal antibodies have markedly improved MM outcomes since the early 2000s. However, patients refractory to these treatments experience abysmal survival.[1] Bispecific antibodies or T-cell engagers (TCE), redirect T cells toward tumor cells leading to immune-mediated cytotoxicity, and have produced outstanding outcomes in refractory myeloma patients.[2,3] Talquetamab, a G protein-coupled receptor, class C, group 5, member D (GPRV5d)-directed TCE, and teclistamab, a B-cell maturation antigen (BCMA)-directed TCE, are both first-in-class US Food and Drug Administration (FDA) approved TCE for relapsed myeloma.

While TCE therapy has demonstrated durable responses in relapsed myeloma, it comes at the cost of significant infectious complications.[4] Considering the profound immunosuppressive potential of TCE, guidelines recommend screening TCE recipients for viral infections, including hep-

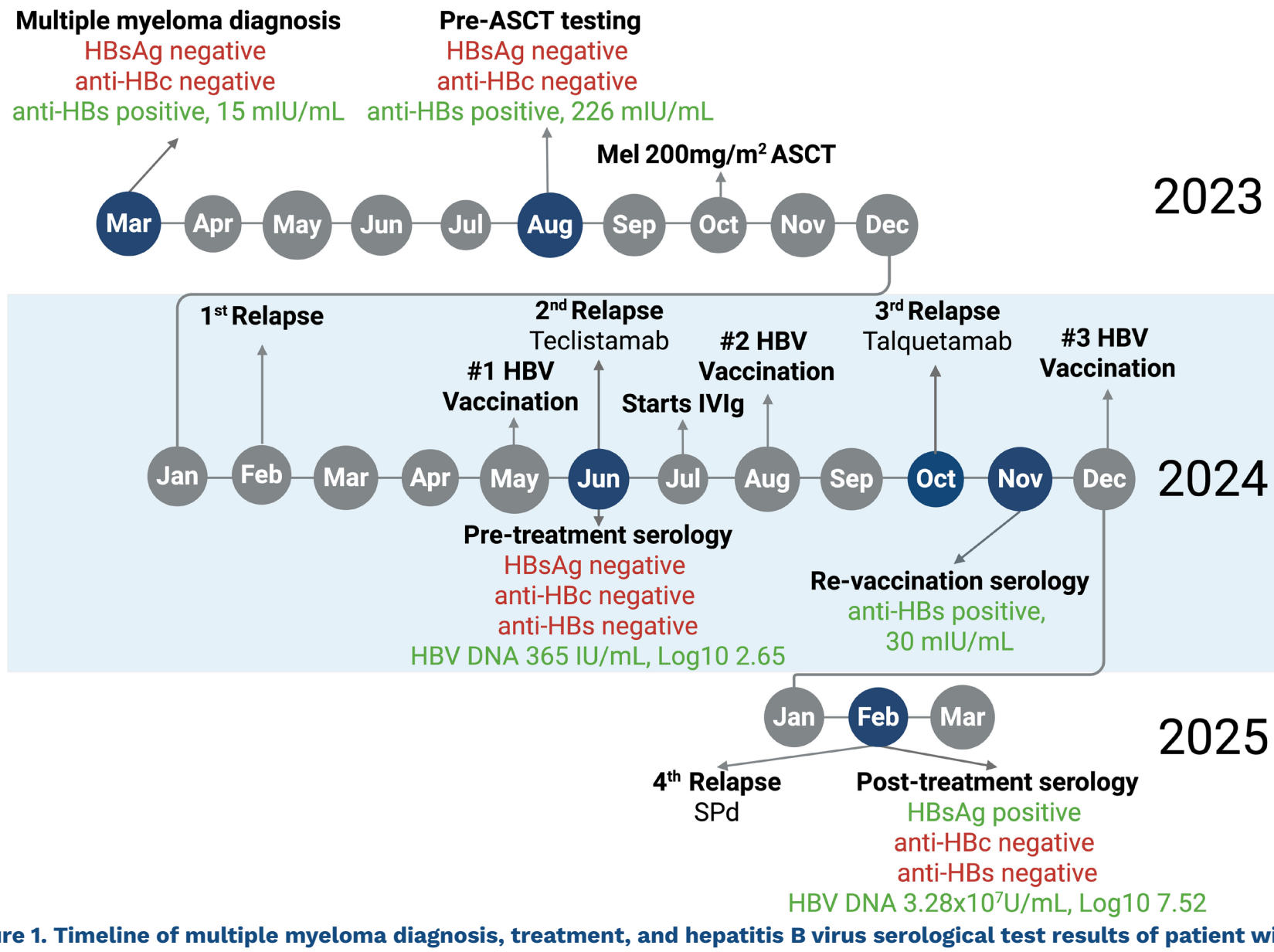

Figure 1. Timeline of multiple myeloma diagnosis, treatment, and hepatitis B virus serological test results of patient with hepatitis B virus reactivation following T-cell engager therapy for multiple myeloma. anti-HB: hepatitis B surface antibody; anti-HBc: hepatitis B core antibody; ASCT: autologous stem-cell transplant; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; IVIg: intravenous immunoglobulin replacement; Mel: melphalan; SPd: selinexor, pomalidomide, dexamethasone.

atitis B virus (HBV).[5] Although viral reactivation following TCE are well described (i.e., cytomegalovirus, progressive multifocal leukoencephalopathy), the risk of HBV reactivation remains unclear, as core-antibody (anti-HBc) positive patients were excluded from key registrational trials, and so the HBV reactivation risk is unknown.[2,3]

We report a 72-year-old man, born in China, with relapsed myeloma (2-prior lines, triple-class refractory) who experienced HBV reactivation despite negative HBV surface-antigen (HBsAg) and anti-HBc Ab following treatment with TCE including teclistamab and talquetamab (Figure 1). Written informed consent was obtained from the patient for the publication of this report. The patient was not known to have HBV and had no recognized exposure throughout his treatment. Serum HBV surface-antibody (anti-HBs) was positive but HBsAg and anti-HBc were negative at diagnosis and before autologous stem-cell transplantation (ASCT), consistent with past vaccination but not past infection. The recommended HBV vaccination schedule was administered post ASCT.

Prior to teclistamab, HBsAg, anti-HBc and anti-HBs were all negative. After relapse following teclistamab, the patient received talquetamab. At relapse following talquetamab, and prior to treatment with selinexor, pomalidomide and dexamethasone, HBsAg became positive, and HBV DNA was detectable. Liver function tests were normal at this time. Look-back HBV DNA testing performed on the pre-teclistamab specimen was positive, despite negative HBsAg and anti-HBc, consistent with occult HBV. The patient received and responded to entecavir therapy.

This is the first case of HBV reactivation post-TCE therapy in myeloma. Individuals with serological evidence of HBV infection (i.e., HBs-Ag or anti-HBc positivity) are at risk of HBV reactivation, with the magnitude of risk determined by the specific immunosuppressive therapy used. ASCT and anti-CD20 monoclonal antibodies are both considered very-high risk therapies, with an over 20% risk of reactivation, while agents such as methotrexate and azathioprine are considered low risk.[6] How drugs within the evolving therapeutic armamentarium for MM will fall on the spectrum of HBV reactivation risk remains to be seen. However, based on the high rate of infectious complications and deaths observed so far in TCE recipients, they are likely to be associated with a high risk of reactivation.[7] For our patient, the exact timing of HBsAg seroreversion is uncertain due to the absence of interim serological testing. However, it is conceivable that reactivation may have occurred much earlier during the course of TCE therapy. In our case, the negative pre-treatment anti-HBc result has major screening implications for patients with hematological malignancies, and, in particular, for patients from endemic areas. We speculate the negative results was a consequence of the patient's underlying hematological malignancy, and the cytotoxic therapy he had received previously. To reduce the risk of HBV reactivation in TCE recipients we recommend that HBV screening for high-risk populations include HBV DNA testing, and that clinicians maintain a high index of suspicion in the setting of abnormal liver function tests on treatment.

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Contributions

MJR, HQ and AT are responsible for study concept. MJR wrote the original draft. All the authors are responsible for data curation and the formal analysis, and reviewed and edited the manuscript.

Data-sharing statement

Data sharing is not applicable to this paper as no datasets were generated or analyzed during the current study.

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