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Review

Preparative Regimen Dosing for Hematopoietic Stem Cell Transplantation in Patients with Chronic Hepatic Impairment: Analysis of the Literature and Recommendations

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A B S T R A C T

Hematopoietic stem cell transplantation (HSCT) is a potentially life-saving therapy for patients with malignant and nonmalignant disease states. Transplant has been associated with high treatment-related morbidity and mortality, therefore limiting its usefulness in patients with baseline liver dysfunction. In the event that a patient with hepatic insufficiency is selected for HSCT, dosage adjustments may be considered; however, no reliable endogenous biomarkers can serve as a guide for adjustments. There is no clear standard or guideline for how to approach these patients, and most adjustments are made empirically on the basis of expert opinion. This article offers practical advice and outlines our personal approaches to provide dosing recommendations for commonly-used preparative agents in the setting of hepatic impairment with the aim to optimize dosing for this patient population.

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is considered to be a potentially life-saving therapy for patients with certain malignant and nonmalignant disease states. In the early days of transplant, treatment-related mortality was high due to infectious complications, organ damage, and graft-versus-host disease (GVHD) [1]. Changes in practice to use less-toxic conditioning regimens for patients with comorbidities have substantially reduced the incidence of treatment-related mortality despite the fact that transplantation is being offered to patients who are older and more seriously ill. Although the overall prevalence of liver complications in the general population has been decreased in recent decades, patients with hepatic impairment may still occasionally present for transplant evaluation [2].

Transplant candidates may present with varying degrees of liver dysfunction due to chronic hepatitis, cirrhosis, or cholestasis [2]. Alternatively, patients may have damage to the liver as a result of previous chemotherapy, or damage may be directly related to their specific neoplastic process [3]. Historically, patients with severe hepatic dysfunction, including those with marginally-compensated cirrhosis (Child-Pugh class B or C), have not been considered suitable candidates for HSCT [4,5]. Reduced-intensity conditioning regimens may lessen the potential for post-HSCT complications in patients with chronic liver disease; however, these patients may still be at risk for decompensation after transplant and have been found to have an increased mortality risk [2,5].

Currently, no endogenous markers can accurately predict hepatic drug clearance and serve as a guide for dosage adjustments for patients with baseline hepatic impairment [3,6]. Without reliable biologic markers of liver metabolism and clearance, there are several general approaches to patients with hepatic dysfunction when dosing chemotherapy [7]. Analysis of the pharmacokinetics of the specific agent may lead to generalizations about the likelihood of toxicity when administered to a patient with chronic liver disease, thus leading to empiric dose adjustments [7]. Dose adjustments should be individualized based on specific indices of liver dysfunction and subsequent pharmacokinetic alterations; however, there is no clear guideline for dose optimization in this patient population. Ideally, if published data are available that analyze the pharmacokinetics of a given chemotherapy agent in a patient population with hepatic insufficiency, adjustments may be recommended based on serum bilirubin, alanine aminotransferase (ALT), and alkaline phosphatase levels [7]. Therapeutic drug monitoring (TDM) in real time is another valid option, when available, because drug concentrations may be altered based on patient-specific metabolism [7].

PHARMACOKINETIC CONSIDERATIONS IN PATIENTS WITH LIVER DISEASES

Optimal chemotherapy dosing for patients with chronic hepatic impairment is still largely unknown due to difficulties with balancing the need for systemic exposure versus the potential for harm with narrow therapeutic windows [3,7,8]. In addition, medications with primarily renal elimination may still prove problematic in cirrhotic patients who

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often demonstrate decreased renal clearance despite a low or normal serum creatinine value [6].

Hepatic insufficiency may lead to decreased metabolism of certain antineoplastic agents that undergo hepatic biotransformation to either active metabolites or resulting in detoxification [3]. Cyclophosphamide (CY) requires activation to an alkylating metabolite by the liver and has no intrinsic alkylating activity before biotransformation [9]. Patients with impaired liver function have a reduced biotransformation rate, and accumulation may potentially occur in this patient population [9]. An increase in adverse events has not been observed in patients with impaired liver function who receive CY; therefore, it may be inferred that toxic effects are attributable to metabolites [10].

Reports in the published literature describe patients who underwent successful allogeneic HSCT in the setting of hepatic impairment [11]. However, the literature consists of mostly case reports including patients with only moderate liver dysfunction. In addition, administration guidelines have focused on patients with liver cirrhosis or fibrosis and not on patients with increased transaminases and/or cholestasis [12]. Therefore, the available pharmacokinetic data are far from complete.

ASSESSMENT OF HEPATIC DYSFUNCTION

Before transplantation, evaluation of liver function should aim to detect the presence of liver disease through patient history, physical examination, and a comprehensive liver panel including serum aspartate aminotransferase, ALT, bilirubin, albumin, and prothrombin time [5]. Hepatitis workup should include testing for hepatitis B e antigen, anti-hepatitis B e antibody, and hepatitis B virus (HBV) DNA. The level of HBV DNA should also be quantified, if positive [13]. Patients in whom liver dysfunction is identified should undergo further workup, including liver imaging and biopsy, as clinically indicated, to assess for the presence of fibrosis or cirrhosis [5,13]. Liver biopsy should also be considered if there is clinical suspicion of cirrhosis or extensive fibrosis, especially when risk factors for cirrhosis are present [14]. If cirrhosis is identified based on imaging ± biopsy, myeloablative conditioning regimens are strongly discouraged.

Patients with Cirrhosis

Patients with pre-existing cirrhosis or established hepatic fibrosis on biopsy are at high risk for severe sinusoidal obstruction syndrome (SOS), multiorgan failure, and fatal hepatic decompensation after transplantation, even with the use of nonmyeloablative regimens [4,5,14,15]. By selecting less liver-toxic agents for the conditioning regimen, the risk of SOS may be lessened and the chance for survival improves [4]. Myeloablative and reduced-intensity conditioning regimens are typically considered to be contraindicated in patients with minimally compensated cirrhosis because of the risk for post-transplant liver complications [2,4,5]. For patients with well-compensated cirrhosis, use of a nonmyeloablative regimen, a regimen that does not contain a high dose of CY or total body irradiation (TBI), or substituting a non–liver-toxic drug for CY may all be valid approaches [14].

Patients with Hepatitis

Although the risk for hepatitis transmission through blood products is quite small in the present day, many patients still present for transplantation with previous exposure to hepatitis viruses [13]. Reactivation may be a late complication of HSCT, rising by 9% to 13% per year of survival after transplantation, with a cumulative probability of 43% at 4 years after HSCT reported in one study [16]. It has been reported that viremia may be triggered after corticosteroid treatment for acute GVHD, antibody to hepatitis B, surface antigen–negative serologic status of the donor, development of chronic GVHD, and loss of protective native antibody to hepatitis B surface antigen after HSCT [2,4,16,17].

Before transplantation, hepatitis viral serology and PCR results should be evaluated to identify patients with hepatitis B or C infection. For patients with latent HBV infection (anti-hepatitis B core antigen positive/HBV DNA-), HBV DNA tests should be used to monitor for viremia [2]. In viremic patients (HBV DNAor hepatitis B surface antigen positive), prophylaxis should be initiated before transplant or upon reactivation in patients with latent infection [2]. The ideal agent either for prophylaxis or preemptive therapy is lamivudine [7]. Lamivudine has been shown to be effective at reducing the incidence of post-HBV as well as HBV exacerbations and should be continued for a minimum of 1 year post-HSCT [14,18,19]. Additionally, lamivudine should not be discontinued until all immunosuppressive agents have been discontinued [15]. HBV-infected patients should also receive HSCT from an HBV naturally immune donor, when possible [8,14,20]. Post-transplant, patients at increased risk for HBV reactivation based on independent predictors should frequently undergo HBsAg, HBsAb, and HBV viral load assessment to detect reactivation should it occur [16].

Most patients with hepatitis C viral infection who undergo HSCT will develop chronic hepatitis; however, in the first 10 years after transplant, the liver-related morbidity is typically minimal [4]. Long-term survivors with chronic hepatitis C should be considered for antiviral therapy such as interferon-alfa, which can be safely administered after discontinuation of all immunosuppressive agents for a least 6 months if there is no evidence of GVHD or myelosuppression [13].

Patients with Ascites

Chemotherapy administration may prove problematic in patients with pleural effusions or ascites [7,21]. Hydrophilic agents, such as fludarabine, may exhibit third spacing into the ascitic fluid, increasing the volume of distribution and potentially resulting in prolonged drug exposure [7]. Mahadevan et al. [21] reported a case of 1 patient who received fludarabine for treatment of follicular lymphoma in the setting of pleural fluid accumulation. This patient developed neutropenia and associated septicemia 2 weeks after fludarabine administration, presumably due to prolonged drug exposure [21]. No data indicate that an empiric dosage adjustment may be effective. In the setting of ascites, draining of pleural fluid or ascites is recommended before fludarabine administration. These patients should also be closely monitored for prolonged toxicities due to the possibility for drug accumulation [7,21].

POTENTIAL FOR LIVER TOXICITY POST-TRANSPLANT

Sinusoidal Obstruction Syndrome

Liver damage, including SOS, is a well-documented complication post-transplant, developing in approximately 20% to 40% of patients receiving more toxic myelosuppressive regimens [8]. This potentially fatal complication after HSCT consists of a variety of clinical and pathologic findings including jaundice, fluid retention, and painful hepatomegaly [8,15]. Clinical criteria for a diagnosis of SOS have been developed by both the Seattle and Baltimore groups