THE RISK OF BK-HEMORRHAGIC CYSTITIS IN THE ERA OF POST-TRANSPLANTATION CYCLOPHOSPHAMIDE

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BK polyomavirus hemorrhagic cystitis (BK-HC) causes substantial morbidity after allogeneic hematopoietic cell transplantation (HCT) but the risk factors for this complication are insufficiently understood. Specifically, the contributions of cyclophosphamide (Cy) administered pre- versus post-transplant (PTCy), and the impact of donor-recipient HLA-disparity, have not comprehensively been assessed. We therefore retrospectively analyzed all consecutive allogeneic HCTs performed at Fred Hutch from 2007-2022 to delineate BK-HC risk factors in multivariable logistic models.

A total of 3,397 allogeneic HCTs were included in the analysis; 91% were performed for hematologic malignancies and 9% for non-malignant conditions. Sixty-six percent had myeloablative and 34% reduced-intensity conditioning. The donors were HLA-matched related (MRD; 30%); matched unrelated (MUD; 51%); mismatched unrelated (MMUD; 12%); and haploidentical related (Haplo; 7%). PTCy-based GVHD-prophylaxis was used in 14%.

The overall incidence of BK-HC (defined as being symptomatic, having macro-hematuria after platelet engraftment, and viruria >107/mL) was 5.4%. In patients not given PTCy, the multivariable risk of BK-HC increased with increasing donor-recipient (D/R) HLA-disparity relative to MRD recipients: MUD, odds ratio (OR), 1.58 (95% confidence interval [CI], 0.95-2.65; p=0.08); MMUD, 2.14 (1.13-4.04; p=0.02). Use of PTCy further increased the risk in most groups: MRD, 6.14 (2.15-17.5; p<0.001); MUD, 4.58 (2.03-10.3; p<0.001); MMUD, 1.91 (0.24-15.1; p=0.54); Haplo, 15.7 (6.74-36.3; p<0.001). While conditioning intensity, use of pre-transplant Cy, stem cell source, and D/R CMV serostatus were not associated with an increased BK-HC risk in multivariate analysis, busulfan-based conditioning was associated with an increased risk (OR, 3.64 [1.32-9.52; p=0.012]).

In conclusion, in addition to D/R genetic disparity and busulfan conditioning, PTCy, but not pre-transplant Cy, are independently associated with an increased risk of BK-HC. Hence, PTCy-mediated delayed immune reconstitution rather than Cy metabolite-mediated urothelial toxicity may account for the relatively high BK-HC risk following PTCy. Therefore, strategies aimed at optimizing the PTCy dose without compromising its GVHD-protective effects are warranted.