

# Severe Refractory Hemorrhagic Cystitis after Hematopoietic Cell Transplantation Responds to Recombinant Human Keratinocyte Growth Factor (KGF) - A Case Report and Review of the Literature

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Severe Refractory Hemorrhagic Cystitis after Hematopoietic Cell Transplantation Responds to Recombinant Human Keratinocyte Growth Factor (KGF) - A Case Report and Review of the Literature

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## To the Editor:

Refractory hemorrhagic cystitis (HC) after allogeneic hematopoietic cellular therapy (HCT) is associated with significant morbidity and non-relapse related mortality, whether it develops within a few days of the

preparative regimen or after engraftment in the setting of urotropic viruses.<sup>1,2</sup> Severe HC includes gross blood and clots (grade 3) and thrombi that require manual clot evacuation (grade 4)(**Supplemental Table 1**). Currently, there are no standard treatments for refractory grade 3 or 4 HC after HCT.

We present a 16 -year-old male who underwent a matched sibling donor bone marrow transplant for myelodysplastic syndrome with a busulfan and cyclophosphamide myeloablative conditioning regimen. Grade 3 HC developed within 24 hours after cyclophosphamide completed (day 0). His infectious work-up at diagnosis, including BK and adenovirus virus were negative at that time. His HC was attributed to cyclophosphamide though he received MESNA and appropriate hydration. He developed autoimmune hemolytic anemia on day +37 which was treated with methylprednisolone, rituximab, sirolimus, and daratumumab. He remained transfusion dependent due to his ongoing AIHA and HC, which persisted despite hyperhydration and supportive care with phenazopyridine and oxybutin. On day +54 post HCT, he was noted to have BK viruria and, despite intravenous cidofovir, had progressive grade 4 HC on day + 62 requiring cystoscopy and manual clot evacuation. His HC was treated with ciprofloxacin, estrogen, and intravesicular cidofovir. Despite these interventions, he had persistent grossly bloody urine with large clots and required an additional 2 manual clot evaluations and cystoscopies. Red blood cell transfusions were required daily to every other day despite resolution of hemolysis markers with anemia and were attributed to HC. On his 6<sup>th</sup> re-admission for supportive care for refractory HC (total days inpatient 91), novel therapies were considered due to lack of response to published therapies and diffuse hemorrhage in the bladder precluding cautery in the setting of physiologic steroids and ongoing cidofovir. In an attempt to avoid bladder toxicity from experimental agents, recombinant human keratinocyte growth factor (rH-KGF) was initiated at 60 mcg/kg three times a week based on limited clinical data.<sup>3,4,5</sup> Within 48 hours of the first rH-KGF dose, his hematuria improved to grade 2 and he became transfusion independent. Over the next 2 weeks, his hematuria improved to grade 1, with full resolution of HC 17 days after his first dose of rH-KGF. Of note, systemic steroids for his AIHA had been weaned to physiological dosing 36 days prior to initiation of rH-KGF and BK viruria was downtrending significantly at the time of starting rH-KGF. While it is possible that HC resolution was unrelated to the drug, given the temporal relationship and lack of prior response to other agents, this is unlikely. From transplant day until completion of rH-KGF he received a total of 85 PRBC units; after resolution of HC, he remained RBC transfusion independent. He is 1 year post HCT and completely recovered without urinary symptoms though he has persistent mild chronic kidney disease (**Figure 1**).

HC is a well-known complication following hematopoietic stem cell transplant (HCT).

The incidence of HC post-HCT is increasing, in part due to increasing application of haploidentical HCT, and there is no consensus to guide the best therapy severe refractory grade 3 or 4 HC, though data support attempting bladder irrigation, intravesicular therapy, estrogen, hyperbaric oxygen therapy.<sup>6,7</sup> Additional therapies such as cidofovir or T cells targeting BK have been employed for viral associated HC.<sup>8</sup> Intravesical irrigation with agents such as formalin, alum, and prostaglandin may be considered, but have limited data to support use and may be associated with short and long term effects including altered mental status, refractory bladder spasms, renal failure, and urinary incontinence.<sup>9,10</sup>

rH-KGF is FDA approved to reduce severe oral mucositis in patients with hematologic malignancies HCT patients, but has been used off label as a rescue agent in severe, refractory HC cases. rH-KGF binds to KGF receptors, resulting in proliferation, differentiation, and migration of epithelial cells. KGF receptors have been reported to be present on areas such as the tongue, esophagus, stomach, liver, kidney, and bladder.<sup>11</sup> Studies in rats have demonstrated that administration of recombinant human KGF results in proliferating cell nuclear antigen expression along the basal layer of urothelium and protection against cyclophosphamide-induced ulcerative HC.<sup>3,12</sup> Given that HC is characterized by damage, inflammation, and bleeding to the bladder mucosa, rH-KGF has been used for its urothelium related restorative properties in 2 other published severe, refractory HC cases (**Table 1**)<sup>4,5</sup>

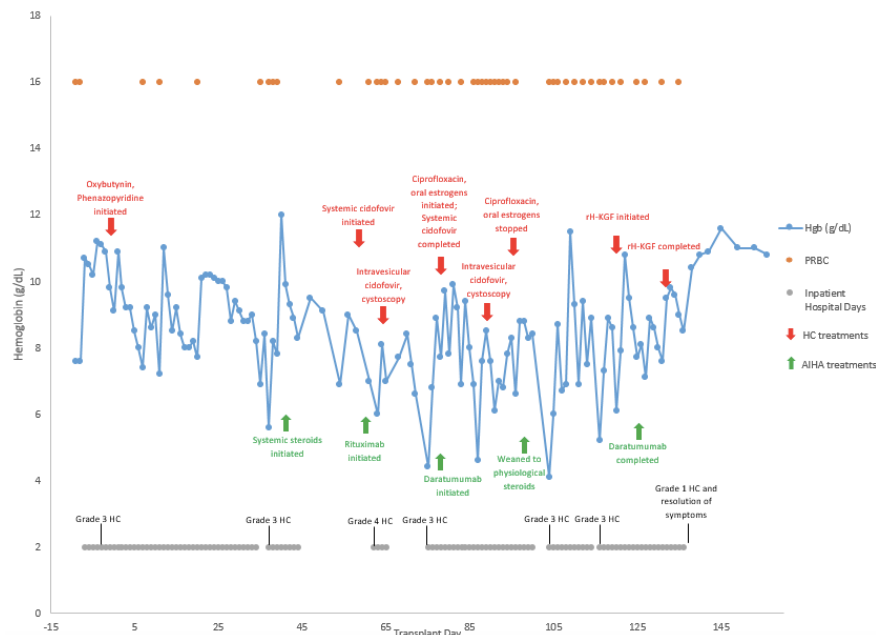
In summary, we report rapid response of severe, refractory HC to rH-KGF in a child post HCT and add to the limited data on this subject. Given a favorable side effect profile, particularly compared to more invasive approaches like intra-vesicular administration of scarring agents, consideration of this drug is merited in

severe, refractory HC.

**Table 1. Summary of Evidence of Use of Keratinocyte Growth Factor for Treatment of Hemorrhagic Cystitis Post Stem Cell Transplant**

Reference	Subject(s)
Ulich TR et al. <sup>3</sup>	15 male Sprague Dawley rats given cyclophosphamide
Czibere A et al. <sup>4</sup>	24-year-old male with refractory T-acute lymphoblastic leukemia given conditioning with fludarabine,
Bhaskaran S et al. <sup>5</sup>	12-year-old female with relapse acute myeloid leukemia given conditioning with busulfan, cyclophosph

**Figure 1: Treatment Course of Patient with Severe, Refractory Hemorrhagic Cystitis and Responses**



Treatment of an adolescent with severe, refractory hemorrhagic cystitis (HC). Despite aggressive treatment of HC with supportive care, cidofovir when BK virus detected, ciprofloxacin, estrogen and 2 manual clot evacuations with intravesicular cidofovir, he remained symptomatic with significant pain, bleeding, and red cell transfusion dependent. After treatment with human keratinocyte growth factor, his refractory HC improved, and ultimately resolved.

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