

Hemorrhagic Cystitis in Allogeneic Stem Cell Transplantation: A Role for Age and Prostatic Hyperplasia

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Abstract

PURPOSE Hemorrhagic cystitis (HC) is a frequent complication during allogeneic hematopoietic stem-cell transplantation (HSCT). HC worsen transplant outcomes and patients wellbeing in terms of pain, medicalization and need for supportive care. Deeper understanding of HC risk factors may contribute to focus on more intense prevention in high risk patients.

METHODS In this report we analyzed 237 consecutive patients who had received HSCT in order to identify possible risk factors for HC and their consequences, focusing on transplant- and gender-related risk factors.

RESULTS HC occurred in 17% of patients, with higher incidence in males (21% vs 11%, $p = 0.03$). Risk factors for HC were age over 55 years, recipients male gender, mismatched-HLA, reduced intensity conditioning and cyclophosphamide-based graft versus host disease (GVHD) prophylaxis. Patients with grade II-IV acute GVHD and detectable BKV and JCV viruria developed more HC. In multivariate analysis, higher age remained independent ($p = 0.013$). Patients with HC experienced longer hospitalization and higher non relapse mortality (NRM). Prostatic hyperplasia (more than 40 cm³) was found in 33% of male patients, who developed HC in 32% of cases (vs 16% in patients with smaller prostates, $p = 0.032$). In male patients, prostatic volume and age were independent risk factors for HC ($p = 0.016$ both).

CONCLUSIONS Age is the major risk factor for HC, with a possible role for cyclophosphamide based GVHD prophylaxis and HLA mismatch. In male population, prostatic hyperplasia is an independent additional risk. As HC is frequent and associates with prolonged hospitalization, more intensive prophylactic strategies could be considered in high-risk subsets.

Introduction

Hematopoietic allogeneic stem cell transplantation (HSCT) is a curative cell therapy for patients with several haematological malignancies. Conditioning chemotherapy may consist in a myeloablative (MAC) or a reduced intensity (RIC) regimen, depending on type of diagnosis, stem cells source and general condition of the patients. Different regimens are known to affect duration and depth of cytopenias and in some cases the extension of the disease control¹. After infusion of stem cells, acute or chronic graft versus host disease (a/c-GVHD) may be observed with different grades of severity. Causes of non relapse mortality (NRM) include multiorgan toxicity, infections and hemorrhages occurring during pancytopenia, and GVHD. Despite usually not fatal, hemorrhagic cystitis (HC) is often observed as a specific toxicity of HSCT. As causes and best treatments for HC are not unanimously defined, this hemorrhagic complication might still be considered as an unmet medical need which impacts heavily on patients hospitalization.

Incidence of HC varies between 12.2% and 36.9% and median occurrence is within the first 30 days. According to literature, major risk factors for HC seem have been identified as pediatric age, myeloablative conditioning and haploidentical or mismatch HLA²⁻⁴. A comparison among matched and haploidentical or mismatch transplants with regards to HC incidence have been tested in 122 patients

homogeneously treated with post-transplant cyclophosphamide (PTCY) as GVHD prophylaxis, reinforcing the concept that HLA matching is a risk factor independently from immunosuppressive regimen (Copelan 2019), while in 161 haploidentical transplants, multivariate risk factors for HC resulted in myelosuppressive conditioning and use of tacrolimus rather than cyclosporine⁵. As far as gender is concerned as a possible risk factor for HC, there is no accordance among studies.

Cyclophosphamide has toxic effects on bladder mucosa. Cyclophosphamide containing conditioning regimens have been reported to be more associated with HC⁶. Moreover, also cyclophosphamide used as GVHD prophylaxis seems to be associated with frequent HC⁷, despite its preferred utilization in haploidentical transplants rather than in matched transplants may generate an important bias.

Despite some studies report higher incidence of HC in non oncologic male population affected by prostatic hypertrophy⁸, there are currently no data available concerning the role of prostatic hypertrophy as a possible risk factor for HC in the setting of HSCT.

In this real life study we aimed to analyze possible unbalance in incidence, severity and duration of HC among genders, and the role of prostatic hypertrophy in the development of HC, compared to other most assessed risk factors.

Patients And Methods

We retrospectively collected data of all 237 consecutive patients who underwent HSCT in our Institution from December 2017 to December 2020. Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI) was calculated for all patients at the moment of hospitalization for HSCT⁹. Almost all patients underwent HSCT for oncological malignancies, while stem cell source derived mainly from matched unrelated and haploidentical donors. These and others patients characteristics are described in Table 1.

The majority of patients (76%) received a myeloablative conditioning regimen (MAC), mostly based on a thiotepa-busulfan-fludarabine (TT-Bu-Flu)¹⁰ or on a fludarabine and 12Gy total body irradiation (Flu-TBI) combination, while 24% of patients received a reduced intensity conditioning (RIC) with fludarabine, cyclophosphamide and 2Gy TBI (Baltimore) or TT-Bu-Flu with reduced doses of busulfan.

Prophylaxis for GVHD was conducted with a triple regimen, with cyclosporine and mycophenolate mofetil associated either with post-transplant cyclophosphamide (PTCY) (79%) or methotrexate (18%). With the exception of severe aplastic anemias, from April 2019 GVHD prophylaxis was homogeneously administered with PTCY for all patients, due to center choice and expertise. Acute and chronic GVHD (aGVHD and cGVHD) was graded according to current criteria 0 to 4 and 0 to 3, respectively¹¹.

Hemorrhagic cystitis was considered as any manifestation of macroscopic hematuria, from pinkish urines to massive emission of clots or acute anemia requiring urgent cauterization or intervention, corresponding to a grade 2 to 4 hematuria according to current literature criteria^{12,13}. For BKV and JCV

determination, a PCR test was performed before conditioning and repeated in cases of urinary symptoms or HC, with the highest-value-ever taken into consideration for statistical analysis.

Prostatic volume and diameters were assessed in males by an expert urologist by revising radiological pre-HSCT imaging when available. Prostatic hyperplasia was radiologically considered of grade 0 when up to 20 cc, then it was graded as follows: grade 1 20–40 cm³, grade 2 40–60 cm³, grade 3 60–80 cm³, grade 4 for more than 80 cm³ in volume¹⁴.

Hemorrhagic cystitis free survival (HC-FS) was counted as time from transplantation to first episode of HC, death or last follow up, censored by occurrence of HC.

Patient related risk factors, namely age, gender, HCT-CI and prostatic volumes in male patients, as well as procedure specific risk factors as HLA matching, GVHD prophylaxis and conditioning regimen, were analyzed in univariate and in multivariate analysis for being associated with higher and earlier incidence of HC with a Cox analysis. Parametric and non parametric categorical variables as well as continuous variables association with HC-FS were tested with Cox regression both for uni and multivariate analysis, censored by occurrence of HC. Differences in medians were evaluated with Welch's test for unequal variances and Student's T test. Survivals were analyzed with Kaplan Meier's curves and non relapse mortality (NRM) was calculated with Cumulative Incidence method. Statistical analysis was performed with NCSS Statistical Software.

Results

The median onset of HC was day 8 after stem cells infusion. Median age was higher in patients experiencing HC (55 vs 61.5 years, $p = 0.002$). When setting a cutoff up to 55 years, in accordance with the median age of our population, we found an increased risk of HC for elderly patients (6% vs 26%, $p < 0.001$). Male patients developed HC in 21% of cases, compared to 11% of females ($p = 0.03$). At day 30, HC-FS was consistently better for females compared to males (91% vs 80%, $p = 0.03$), with a plateau after the first month.

The great majority of patients underwent HSCT for hematological malignancies, with different onsets of HC showed in Table 1. HC occurred in 15% patients affected by acute malignancies and in 22% patients affected by chronic diseases as myeloproliferative neoplasms and lymphomas ($p = 0.19$). There was no difference in incidence of HC according to HCT-CI. We observed poorer HC-FS in patients receiving RIC than MAC (14% vs 25%, $p = 0.03$). As a notice, patients treated with Flu-TBI MAC regimen experienced no HC: in this subset, all patients were affected by ALL, and aged 45 years or less.

We then compared HC in HLA identical (sibling and unrelated) vs haploidentical transplants, finding more HC in the latter (12% vs 28%, $p < 0.001$). In detail, the incidence of HC was 6%, 15% and 28% for sibling, matched unrelated and haploidentical donors, respectively.

Patients who received GVHD triple prophylaxis with PTCY experienced HC in 20% of cases, compared to 2% of HC in patients who received triple GVHD prophylaxis with MTX ($p = 0.02$). As two out of five patients with severe aplasia experienced HC, we found 40% HC in this setting.

In multivariate analysis, age more than 55 alone remained an independent risk factor for HC, with an Hazard Ratio (HR) of 3.06 (95% CI 1.26–7.39).

Overall, 195 (82%) and 39 (18%) patients experienced grade 0–1 or 2–4 acute GVHD, respectively. Patients with grade 0–1 aGVHD had less HC compared to those with grade 2–4 aGVHD (13% vs 29%, $p = 0.011$).

We tested 219 patients for BKV and JCV viremia, which was found positive, anytime during hospitalization, in 18% and 39% of cases, respectively. Patients with no viral reactivation had less HC compared to those with detectable BKV or JCV in urines (15% vs 33% $p = 0.006$ for BKV and 13% vs 25% $p = 0.022$ for JCV). Among the 29 patients with both BKV and JCV found positive in urines, 12 (41%) experienced HC. We found no correlation between prostatic hyperplasia and detection of BKV or JCV in urines.

Median duration of HC was 7 days (range 1–85 days): treatment for HC consisted in adequate hydration and platelets transfusions for all patients; some patients required more intensive treatments consisting in continuous bladder irrigation (55% of HC), specific antiviral therapy with cidofovir (7%), endoscopic diathermocoagulation (10%) or intravesical instillations with Platelet-Rich Plasma (3%) or hyaluronic acid (3%). Non relapse mortality was significantly higher for patients with HC ($p = 0.001$), both six month (8% vs 25%) and one year (12% vs 38%) after transplant (Fig. 1). For those who were successfully discharged, median duration of hospitalization was higher for those with HC (26 vs 36 days, $p = 0.05$).

We then moved to analyze male population in order to assess the possible role of prostatic volumes. Age more than 55 was confirmed to be associated with higher HC ($p < 0.001$), together with HLA mismatch ($p = 0.008$) and PTCY based triple GVHD prophylaxis ($p = 0.04$).

Median prostatic volume was greater in patients who experienced HC (25 vs 32 cm^3 , $p = 0.02$). Patients with at least grade 2 prostatic hyperplasia (more than 40 cm^3) experienced HC in 32% of cases, compared to 16% in those with prostatic volume less than 40 cm^3 ($p = 0.03$). As expected, age and prostatic volume were strongly correlated ($p < 0.001$). In multivariate analysis age over 55 and prostatic volume remained the only independent risk factors for HC ($p = 0.016$ both).

Discussion

In HSCT patients, hematuria is generally considered related to toxic or infectious impairment of urinary mucosae until proven otherwise, and “hematuria” and “hemorrhagic cystitis” are widely used as synonyms. In this study we aimed to verify the risk potential of patients and transplants characteristics in the development of HC.

In our cohort, HC was strongly associated to age both as a continuous increasing risk and with a cut off of at 55 years. The widest available retrospective analysis performed on 1321 patients of all ages identified age lower than 20 years old as being at higher risk of HC ¹³, whether the biggest prospective study on 450 patients did not find differences in HC from being younger or older than 18 years, despite an incidence of HC in 21% of younger patients compared to an average of 12.2% ³. At the best of our knowledge, there is no other data analyzing the older age as a risk factor for HC in an exclusively adult population.

Cyclophosphamide has been described as having a role in HC when used in conditioning regimens ¹³. The rationale of this association lies in acrolein, a cyclophosphamide urinary metabolite with toxic effects on bladder mucosae. As some data are available on risk of HC in PTCY treated patients, no comparison has been made between the two triple prophylaxis regimens with post-transplant methotrexate or cyclophosphamide until now. In our population, we report that PTCY treated patients experience more HC, despite not independently from age.

Moderate-to-severe aGVHD was associated to more HC in our population, in partial disagreement to what had been described in 2015 in a small French cohort, where 22 out of 33 haploidentical transplants treated with PTCY experienced HC with no association with GVHD ⁷. It is possible to hypothesize a role for GVHD in damaging urothelium together with direct or indirect effects of GVHD therapy with high dose steroids and immunosuppression.

Matched transplants had a lower incidence of HC compared to haploidentical transplants. This is similar to what Copelan and colleagues had described in 122 patients uniformly treated with PTCY prophylaxis, where they reported HC in 25% vs 42% of HLA matched and haploidentical transplants, respectively. In that series the authors hypothesized that HLA mismatched donor T cells could impair host antigen presenting cells, thus favoring BKV infections ⁴. A strong association between HC and BKV detection has been found also in our cohort of patients and was independent from the other risk factor (data not shown). Similarly, Oltolini et al have reported 235 patients who received PTCY as GVHD prophylaxis, where HLA mismatch was found to favor early viral, but not bacterial, infections ¹⁵. As this immunological thesis appears interesting, it does not fully explain higher impact of HLA mismatch in BKV negatives HCs.

About the role of gender in development of HC, few and contrasting literature is available: Gargiulo et al found no difference in HC incidence in a prospective population of 450 mixed pediatric and adult patients of both genders (13% vs 11%), while Lunde et al retrospectively revised 1321 consecutive patients and found that male gender was associated with higher incidence of HC (15% vs 23%, $p = 0.01$) ^{3,13}. In our study, male patients had doubled incidence of HC compared to females. We found that HC was more common as prostatic volume increased and that a cut off of 40 cm³ was able to discriminate two populations with very different HC risk (16% vs 32%, $p = 0.03$). Despite association between age and prostatic hyperplasia results obvious, they seem to remain independently associated to HC in multivariate analysis. We argued that prostate may play a part in determining incidence and severity of HC in male

patients. Our hypothesis was that toxic metabolites as acrolein may have a prolonged contact with bladder mucosae due to urinary retention in patients with prostatic hyperplasia. This exposure could reasonably contribute to chemical damage and bleeding in a thrombocytopenic and immunocompromised patient. Moreover, urinary retention may enhance viral damage from JCV and BKV on urothelium. Prostatic samples from patients with prostate cancer (PC) and prostatic hyperplasia have been found to be a reservoir both of BKV and JCV in 22–32% cases as well as a possible site of viral replication^{16,17}. As urinary viral reactivation, especially BKV, are common in several immunodeficiency status, and polyomavirus in urinary tract may contribute to HC, it is reasonable to hypothesize that prostatic hyperplasia, viral reactivation and HC may be connected^{18,19}.

Patients with HC had worse outcomes. Not only they experienced more prolonged hospitalization, but they also had higher probability of dying for NRM. Prolonged hospitalization was usually due to HC, as far as its acute management requires invasive procedures and an intense transfusion support. On the other side, multi organ worsening condition may associate with infections, severe cytopenia or renal failure, thus identifying HC as the top of an iceberg.

A point of discussion is HC prophylaxis: from GITMO prospective experience and ECIL guidelines on BKV related HC, some prophylactic approaches have been recommended despite no clear efficacy have been demonstrated. In those papers, Mesna associated to cyclophosphamide, urine alkalinization, intravenous hyper-hydration and bladder continuous irrigation are considered, while no clear position is taken on antibiotic prophylaxis^{3,20}. In 2008 Hadjibabaie et al performed continuous bladder irrigation on 40 consecutive patients receiving HSCT for sibling donor and conditioning including cyclophosphamide, and were compared to an historical cohort. Incidence of HC was 50% in historical cohort vs 32% in patients receiving prophylactic irrigation ($p = 0.1$), with lower length of HC when occurred (18 vs 10 days)²¹. In our population, three patients received continuous bladder irrigation for a history of intolerance to Mesna or previous HC, and none of them experienced HC. At present days, treatment of HC is not formally standardized in the setting of allogeneic transplants, although factors as time from transplant and platelets recovery seem to play a central role. Most patients usually receive intravenous hyper-hydration and intensive platelets transfusion, with continuous bladder irrigation limited to 12–27% patients according to different experiences^{13,20}. Limited amount of patients require intravesical cauterization or intravesical instillation of hyaluronic acid, fibrin glue or platelet-rich plasma. When viral BKV is detected, systemic or local specific therapy is required and can be curative in up to 70% cases. A possible role may be played by BKV genotype, while the role of JCV need to be further investigated^{22,23}.

Data on prostatic hyperplasia have never been reported in this setting: a prospective evaluation of post void residual urine and measurement of acrolein and viruses in urines may clarify the pathogenesis of this complication.

In conclusion, age more than 55 is the an independent risk factor for hemorrhagic cystitis in patient treated with allogeneic stem cell transplantation. Mismatch transplants and PTCY based triple GVHD prophylaxis may have a role, but not independently from age. For male patients, prostatic hypertrophy

may be an additional risk factor. More intense prophylactic strategies may represent a reasonable option to prevent HC in the setting of high risk adult transplants.

Declarations

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Conflicts of interest/Competing interests: the authors declare no relevant conflict of interests nor competing interests

Availability of data and material: for access to data, please contact the corresponding author.

Code availability: Analysis were performed via NCSS Statistical Software

Authors' contributions: EG FS LDG and SS designed the study and drafted the paper. EM SG EG LDG FS AML PC and AB provided clinical data. LL II AA SS and AB critically reviewed the paper

Ethics approval: This study has been performed in accordance with the ethical standards of the 2000 Declaration of Helsinki as well as the 2008 Declaration of Istanbul

Consent to participate All patients had provided written informed consent for non interventional research utilization of their anonymized data.

Consent for publication: not applicable (no personal images)

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Tables

Table 1: Characteristics of patients of both genders with uni and multi-variate analysis for HC.

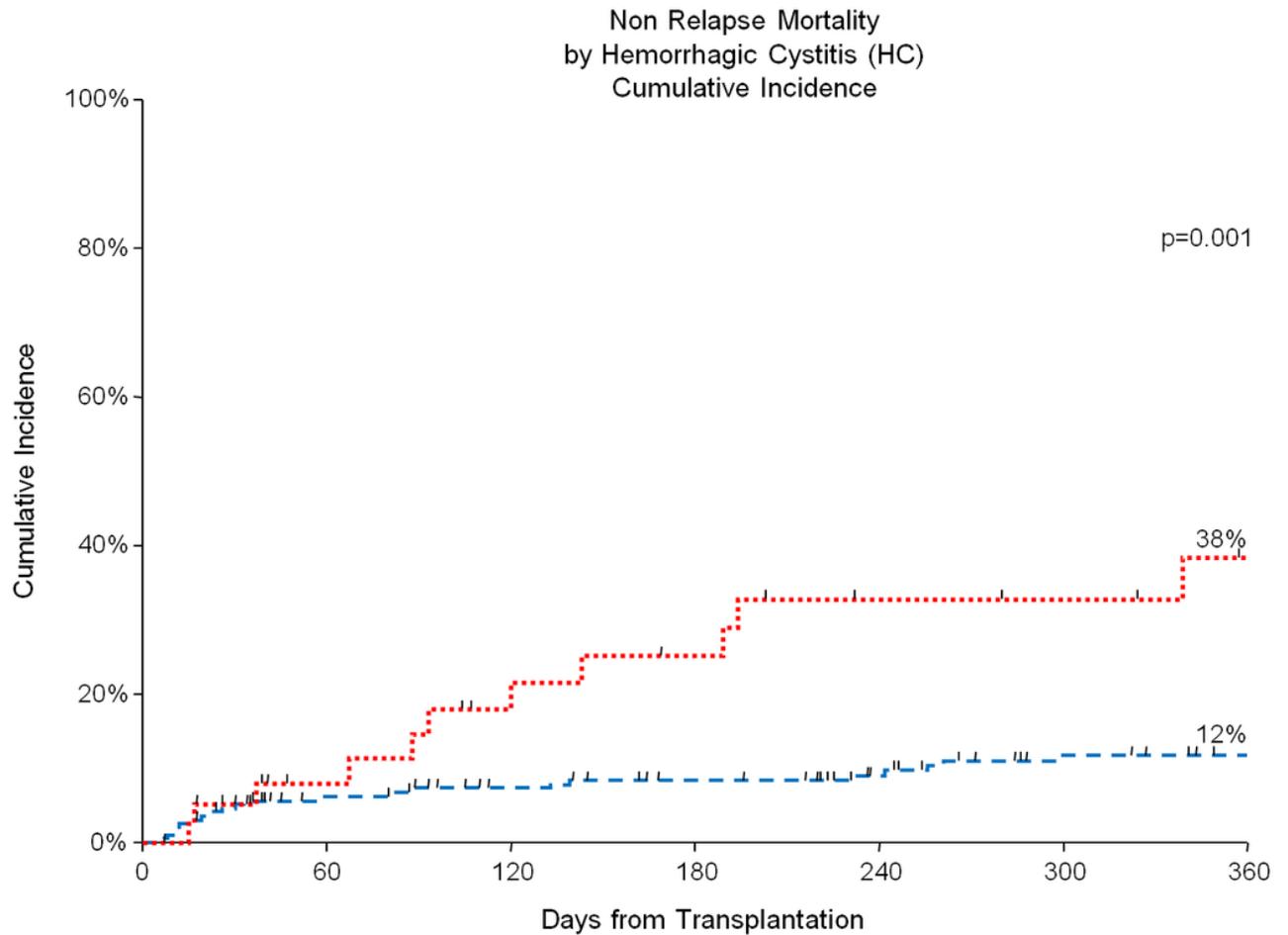
Major hematological and demographic characteristics of patients are shown in this table and compared to HC-FS through Cox analysis. Only variables with univariate p values of 0.05 or less acceded to multivariate analysis.

Legend: AML acute myeloid leukemia; ALL acute lymphoid leukemia; MPD myeloproliferative neoplasm; NHL non Hodgkin lymphoma; HL Hodgkin lymphoma; AA aplastic anemia; MDS myelodysplastic syndrome; HCT-CI Hematopoietic cell transplantation-specific comorbidity index; MSD matched sibling donor; MUD matched unrelated donor; TT-Bu-Flu tepadine, busulfan and fludarabine; Flu-TBI Fludarabine and Total Body Irradiation; GVHD graft versus host disease; MTX methotrexate; PTCY post transplant cyclophosphamide.

Figures

		Patients	Without HC	With HC	Univariate analysis	Multivariate analysis	HR (95%ci)
			n(%)	n(%)	p value	p value	
Total		237	197 (83)	40 (17)			
Diagnosis	AML	101	84 (83)	17 (17)			
	ALL	30	27 (90)	3 (10)			
	MPN	54	41 (75)	13 (25)			
	NHL	17	15 (88)	2 (12)			
	HL	3	3 (100)	0 (0)			
	AA	5	3 (60)	2 (40)			
	MDS	27	24 (89)	3 (11)			
Chronic vs Acute diseases	LH LNH MPN AA	79	62 (78)	17 (22)	0.19		
	AML ALL MDS	158	135 (85)	23 (15)			
HCT-CI	Missing data	7			0.33		
	0-1	67	58 (87)	9 (13)			
	>1	163	133 (82)	30 (18)			
Recipient age	median	56	55	61.5	0.002		
	Up tp 55	109	102 (94)	7 (6)	<0.001	0.013	3.06 (1.26-7.39)
	Over 55	128	95 (74)	33 (26)			
Recipient gender	Females	102	91 (89)	11 (11)	0.034	0.25	1.56 (0.73-3.33)
	Males	135	106 (79)	29 (21)			

HLA matching	MSD	53	50 (94)	3 (6)			
	MUD	102	87 (85)	15 (15)			
	Haplo	75	54 (72)	21 (28)			
	CB	7	6 (86)	1 (14)			
Matched vs haplo	MSD and MUD	155	137 (88)	18 (12)	<0.001	0.11	1.94 (0.86-4.35)
	Haplo	75	54 (72)	21 (28)			
Conditioning regimen	Missing	6					
	TT-Bu-Flu	190	156 (82)	34 (18)			
	Baltimore	24	19 (79)	5 (21)			
	Flu-TBI	17	17 (100)	0 (0)			
	Other	5	3 (60)	2 (40)			
RIC vs MAC	MAC	180	154 (86)	26 (14)	0.032	0.54	1.2 (0.62-2.44)
	RIC	51	38 (75)	13 (25)			
GVHD prophylaxis	Triple MTX based	43	42 (98)	1 (2)	0.02	0.068	6.6 (0.86-47.5)
	Triple PTCY based	188	150 (80)	38 (20)			



Number At Risk								
— —	Without HC	197	171	150	136	121	106	100
.....	With HC	40	27	21	18	13	11	7

Figure 1

Non Relapse Mortality (NRM) and Hemorrhagic Cystitis (HC). Patients with HC (in red) had higher NRM compared to those without HC (in blue), with 8% vs 25% at 6 months and 12% vs 38% at 1 year (p=0.001).