Acquired Cytoresistance in the Setting of Hematopoietic Cell Transplantation

Richard A. Zager

The Clinical Division, The Fred Hutchinson Cancer Research Center, Seattle, Washington; and Department of Medicine, University of Washington, Seattle, Washington

Background and objectives: Pre-existent renal insufficiency is a widely accepted risk factor for superimposed renal damage (*e.g.*, due to ischemia or nephrotoxic drug administration). However, both experimental renal injury and surgical ablation of renal mass in rodents confer protection against superimposed renal insults (the so-called "acquired cytoresistance" state). This study addressed whether baseline renal function is associated with either increased or decreased susceptibility to renal injury in patients undergoing hematopoietic cell transplantation (HCT), a procedure that is widely recognized to induce acute or subacute renal damage.

Design, setting, participants, & measurements: Estimated GFRs (eGFRs; Modification of Diet in Renal Disease formula) were assessed at baseline and approximately 1 year after HCT in 1216 patients who were transplanted at the Fred Hutchinson Cancer Center between 1991 and 2002. The frequency of a renal functional decline (arbitrarily defined, *a priori*, as ≥25% loss of baseline eGFR) and absolute reductions in eGFR (in ml/min) were calculated.

Results: Both the frequency and degree of post-HCT eGFR reductions directly and linearly correlated with baseline eGFRs (range, 25 to 135 ml/min). Thus, the higher the baseline eGFR, the greater the risk and severity of subsequent loss of renal function ($P < 0.0001$).

Conclusions: These data indicate that reduced baseline renal function is not necessarily a risk factor for post-HCT renal functional declines. Rather, these observations support the concept that "acquired cytoresistance," as seen in experimental animals, may, under selected circumstances, be expressed in the clinical arena.

Clin J Am Soc Nephrol 5: 2150–2153, 2010. doi: 10.2215/CJN.07780910

A seeming paradox exists within the experimental and clinical literature concerning the impact of pre-existent renal injury on renal susceptibility to further damage. On the one hand, the experimental literature is replete with studies that show that induction of either nephrotoxic or ischemic injury confers protection against subsequent ischemic or toxin-mediated renal damage (1–8). This protection is usually attributed to renal tubular injury–induced upregulation of cytoprotective molecules (*e.g.*, heme oxygenase 1) (1–3). However, even surgical ablation of renal mass (*e.g.*, 1½ nephrectomy) (9) or transient ureteral obstruction (10) is sufficient to induce this cytoresistant state (*i.e.*, in the absence of severe proximal tubular injury or tubular cell death). Indeed, the emergence of "cytoresistance" in residual functioning nephrons is an appealing concept from a teleological perspective: it would serve to stave off additional losses of renal function and thereby slow or prevent the development of severe renal failure. In seeming conflict with this experimental literature is the widely held clinical view that pre-existent renal damage sensitizes the kidney to further damage. For example, it is well recognized that reduced renal function is a significant risk factor for radiocontrast media–induced acute renal failure (11,12). Furthermore, reduced renal function is known to increase the risk of aminoglycoside nephrotoxicity and calcineurin-induced renal injury and predispose to renal failure caused by either nonsteroidal anti-inflammatory drugs or angiotensin converting enzyme/angiotensin receptor blocker inhibitors. Given these clinical examples, the relevance of experimental "acquired cytoresistance" to the human condition has remained in doubt.

During the course of an extensive clinical database review of patients who received hematopoietic cell transplants (HCTs) at the Fred Hutchinson Cancer Research Center (FHCRC), an apparent example of human acquired cytoresistance was observed. The purpose of the Expedited Report is to offer this information for consideration.

Materials and Methods

The database consisted of all patients who underwent HCT at FHCRC between 1991 and 2002. Only those patients who survived to 1 year after transplant and for whom estimated GFRs (eGFRs) at baseline and approximately 1 year after HCT (range, 9 to 15 months) could be calculated were included ($n = 1216$). GFR was estimated using the Modification of Diet in Renal Disease equation as follows: eGFR (ml/min per 1.73 m^2) = $186 \times (S_{cr})^{-1.154} \times (Age)^{-0.203} \times (0.742$ if female) $\times$ (1.212 if African American). The protocol that led to the generation of this information was approved by the FHCRC Insti-

Received September 3, 2010. Accepted September 27, 2010.

Published online ahead of print. Publication date available at www.cjasn.org.

Correspondence: Dr. Richard A. Zager, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue N, Room D2-190, Seattle, WA 98109. Phone: 206-667-6549; Fax: 206-667-6519; E-mail: dzager@fhcrc.org

ISSN: 1555-9041/512–2150

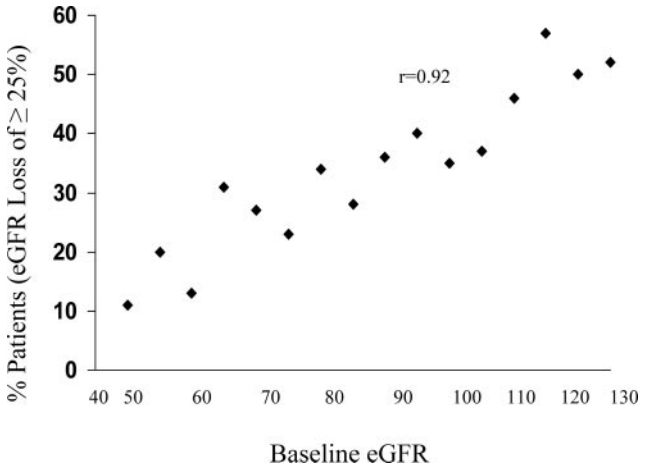

Figure 1. Percent of patients who experienced a ≥25% decrease in their baseline eGFRs at approximately 1 year after HCT. The patients were grouped according to progressive increases of eGFR of 5 ml/min for the purpose of data presentation. As shown, there was a linear relationship between baseline eGFR and the frequency of ≥25% loss of eGFR. The numbers of patients within each subdivision are presented in Figure 2.

tutional Review Board Committee. The database included that which was previously published (13), with the following additions. First, baseline eGFRs were calculated. Second, whereas the previous study (13) excluded patients who had elevated baseline serum creatinine levels (above the normal laboratory range), these patients were included in this study because it was this group of patients who presumably could provide the greatest definition of the impact of baseline renal functional impairment on subsequent responses to HCT. All data are presented as means ± SEM. The data were analyzed by Pearson's correlation using continuous variable baseline and ending eGFR values. For ease of visual presentation, the data were subdivided according to baseline eGFRs in 5-ml/min eGFR increments (*e.g.,* 50 to 55, 55 to 60 ml/min, etc.).

Results and Discussion

Acute kidney injury is a well-known complication of both myeloablative and nonmyeloablative HCT (13–21). Multiple causes for it exist, including radiochemotherapy-induced renal injury, hepatic sinusoidal obstructive syndrome (which causes renal hypoperfusion/intermittent renal ischemia), sepsis syndrome, systemic hypotension, acute graft *versus* host disease, and exposure to nephrotoxic agents (including calcineurin inhibitors, aminoglycoside antibiotics, and amphotericin B) (13–21). Once it develops, post-HCT strongly correlates with both short-term mortality (within 100 days after transplant) and with progressive renal disease. For example, at 1 year after HCT, Hingorani *et al.* (13) reported that 23% of HCT patients manifested stage 4 chronic kidney disease. However, the impact of baseline renal function at the time of HCT on the frequency and severity of this evolving renal injury during the first year after transplant has remained unknown.

We recently had the opportunity to review, and expand on, a database that contained information on 3325 patients who underwent HCT at our institution between 1991 and 2002. Part of this cohort formed the basis for the above-noted report by Hingorani *et al.* (13). However, no baseline eGFR information was available for that study, and thus, neither the frequency nor the degree of renal functional declines could be ascertained. In an effort to obtain information for the design of a future clinical trial, we recently reviewed the FHCRC experience during the above timeframe. Baseline eGFRs and eGFRs at approximately 1 year after HCT were calculated using the four-factor Modification of Diet in Renal Disease formula (22) for all patients for whom the required data inputs were available (n = 1216 individuals). Using baseline eGFR values, two endpoints were established for the purpose of this review. First, the frequency of renal functional impairment was assessed. An arbitrary, *a priori*, definition of a ≥25% reduction of baseline eGFR at 1 year was denoted as post-HCT "renal functional impairment." The frequency of this result for patient groups (divided into groups of 5-ml/min GFR increments) was assessed (*e.g.,* patients with eGFRs of 50 to 55, 55 to 60, 65 to 70 ml/min, etc.). Second, the absolute amount of eGFR loss (difference between starting and ending eGFRs) for each of the patients was assessed. These two analyses yielded striking results. As shown in Figure 1, the frequency of post-HCT renal functional declines was directly related to baseline eGFR. For example, approximately 50% of patients who had a starting eGFR of ≥120 ml/min experienced at least a 25% eGFR reduction by 1 year later. Conversely, for patients with a starting eGFR of 50 to 60 ml/min, only approximately 12% of patients experienced a 25% eGFR decline. This direct relationship between frequency of ≥25% eGFR loss and baseline eGFR was observed across the entire GFR range, as depicted in Figure 1. The second notable result was that absolute GFR loss, in terms of milliliters per minute, was also directly

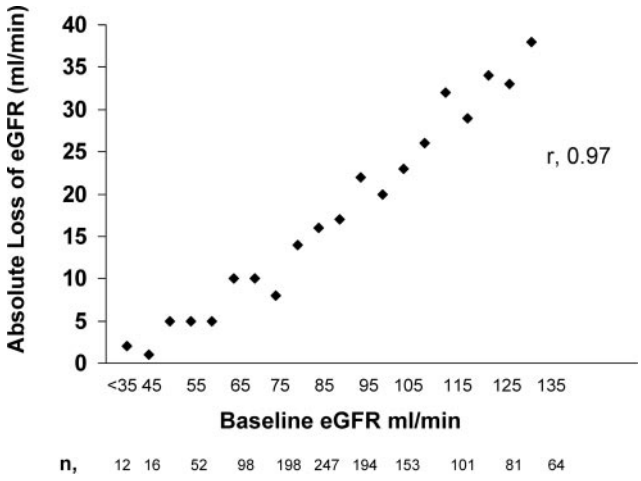

Figure 2. The absolute amount of eGFR loss (baseline − ending eGFR; presented in ml/min). The SEs for each patient groups were as follows: groups with a baseline eGFR of ≥95, SEM ≤2 ml/min; for patients groups between 105 and 115, SEMs were ≤3 ml/min. The SEMs for the remaining groups were 4 to 5 ml/min.

related to baseline eGFR. This is graphically presented in Figure 2. As examples, for those individuals with baseline eGFRs of between 35 and 55 ml/min, the mean absolute eGFR reduction was only 5 ml/min. Three patients had starting eGFRs of between 20 and 35 ml/min, and none experienced a GFR loss of >2 ml/min. Conversely, at the other end of the spectrum, the mean absolute loss of eGFR for patients with starting values of ≥120 ml/min was 38 ml/min. Again, this striking relationship between baseline eGFR and absolute eGFR loss was apparent across the entire baseline eGFR range. Thus, both the frequency of eGFR loss (≥25%) and the absolute amount of eGFR loss (ml/min) provided complementary information. In summary, these data strongly imply that prior renal injury, undoubtedly of diverse etiologies, was associated with stepwise protection against subsequent superimposed renal damage during the first year after HCT. These data seemingly support the concept that pre-existent renal injury can, under selected circumstances, confer a renal cytoresistant state, as suggested by the experimental literature.

Clearly, these results reflect a highly selected patient population: *i.e.,* cancer patients who needed HCT. Furthermore, the combination of post-HCT renal insults that these patients experienced (*e.g.,* conditioning radiation, graft *versus* host disease, hepatic sinusoidal obstruction syndrome, calcineurin inhibition) must be considered unique. Thus, the results of this database review cannot be construed as being applicable to a more broad-based patient population. In addition, two database limitations must be stressed. First, the presented data reflect values that were based on only a single pretransplant and single post-transplant eGFR, rather than recurrent measurements. Second, the limitations of drawing conclusions based on eGFRs, rather than true GFR measurements (*e.g.,* by iothalamate), are well known. Nevertheless, the consistency and linearity of the results, observed in 1216 patients over an 11-year time frame, do support the existence of an acquired cytoresistance state. Indeed, if it was possible to dissect out the factors that give rise to this cytoresistance, new therapeutic strategies for protecting other patient populations from acute renal injury might emerge.

Acknowledgments

I thank Drs. Sangeeta Hingorani and George McDonald for providing database access and Mr. Gary Schoch (FHCRC Biostatistics Program) for performing eGFR calculations and subsequent data analysis. This work was supported by National Institutes of Health Grants DK38432, DK063038, CA18029, and CA15704.

Disclosures

None.

References

1. Honda N, Hishida A, Ikuma K, Yonemura K: Acquired resistance to acute renal failure. *Kidney Int* 31: 1233–1238, 1987
2. Nath KA, Balla G, Vercellotti GM, Balla J, Jacob HS, Levitt MD, Rosenberg ME: Induction of heme oxygenase is a rapid, protective response in rhabdomyolysis in the rat. *J Clin Invest* 90: 267–270, 1992
3. Nath KA: Heme oxygenase-1: A provenance for cytoprotective pathways in the kidney and other tissues. *Kidney Int* 70: 432–443, 2006
4. Bolisetty S, Traylor AM, Kim J, Joseph R, Ricart K, Landar A, Agarwal A: Heme oxygenase-1 inhibits renal tubular macroautophagy in acute kidney injury. *J Am Soc Nephrol* 21: 1702–1712, 2010
5. Bonventre JV: Kidney ischemic preconditioning. *Curr Opin Nephrol Hypertens* 11: 43–48, 2002
6. Elliott WC, Houghton DC, Gilbert DN, Baines-Hunter J, Bennett WM: Gentamicin nephrotoxicity. I. Degree and permanence of acquired insensitivity. *J Lab Clin Med* 100: 501–512, 1992
7. Houghton DC, Lee D, Gilbert DN, Bennett WM: Chronic gentamicin nephrotoxicity. Continued tubular injury with preserved glomerular filtration function. *Am J Pathol* 123: 183–194, 1986
8. Zager RA, Baltes LA, Sharma HM, Jurkowitz MS: Responses of the ischemic acute renal failure kidney to additional ischemic events. *Kidney Int* 26: 689–700, 1984
9. Zager RA, Baltes LA: Progressive renal insufficiency induces increasing protection against ischemic acute renal failure. *Lab Clin Med* 103: 511–523, 1984
10. Zager RA: Obstruction of proximal tubules initiates cytoresistance against hypoxic damage. *Kidney Int* 47: 628–637, 1995
11. Leblanc M, Kellum JA, Gibney RT, Lieberthal W, Tumlin J, Mehta R: Risk factors for acute renal failure: Inherent and modifiable risks. *Curr Opin Crit Care* 11: 533–536, 2005
12. Stone GW, Tumlin JA, Madyoon H, Lepor NE, Mc Cullough PA, Mathur VS, Murray PT, O'Neill WW: Design and rationale of CONTRAST: A prospective, randomized, placebo-controlled trial of fenoldopam mesylate for the prevention of radiocontrast nephropathy. *Rev Cardiovasc Med 2 Suppl* 1: S31–S36, 2001
13. Hingorani S, Guthrie KA, Schoch G, Weiss NS, McDonald GB: Chronic kidney disease in long-term survivors of hematopoietic cell transplant. *Bone Marrow Transplantation* 39: 223–229, 2007
14. Zager RA, O'Quigley J, Zager BK, Alpers CE, Shulman HM, Gamelin LM, Stewart P, Thomas ED: Acute renal failure following bone marrow transplantation: A retrospective study of 272 patients. *Am J Kidney Dis* 13: 210–216, 1989
15. Zager RA: Acute renal failure in the setting of bone marrow transplantation. *Kidney Int* 46: 1443–1458, 1994
16. Fink JC, Cooper MA, Burkhart KM, McDonald GB, Zager RA: Marked enzymuria after bone marrow transplantation: A correlate of veno-occlusive disease-induced "hepatorenal syndrome." *J Am Soc Nephrol* 6: 1655–1660, 1995
17. Hingorani S: Chronic kidney disease in long-term survivors of hematopoietic cell transplantation: Epidemiology, pathogenesis, and treatment. *J Am Soc Nephrol* 17: 1995–2005, 2006
18. Changsirikulchai S, Myerson D, Guthrie KA, McDonald GB, Alpers CE, Hingorani SR: Renal thrombotic microangiopathy after hematopoietic cell transplant: Role of GVHD in pathogenesis. *Clin J Am Soc Nephrol* 4: 345–353, 2009
19. Chang A, Hingorani S, Kowalewska J, Flowers ME, Aneja

T, Smith KD, Meehan SM, Nicosia RF, Alpers CE: Spectrum of renal pathology in hematopoietic cell transplantation: A series of 20 patients and review of the literature. *Clin J Am Soc Nephrol* 2: 1014–1023, 2007

20. Weiss AS, Sandmaier BM, Storer B, Storb R, McSweeney PA, Parikh CR: Chronic renal disease following non-myeloablative hematopoietic cell transplantation. *Am J Transplant* 6: 89–94, 2006
21. Ando M, Mori J, Ohashi K, Akiyama H, Morito T, Tsuchiya K, Nitta K, Sakamaki H: A comparative assessment of the RIFLE, AKIN and conventional criteria for acute kidney injury after hematopoietic SCT. *Bone Marrow Transplant* 28: 376–380, 2010
22. Manjunath G, Sarnak MJ, Levey AS: Prediction equations to estimate glomerular filtration rate: An update. *Curr Opin Nephrol Hypertens* 10: 785–792, 2001