Alveolar Hemorrhage and Acute Graft-versus-Host Disease.

Philippe Ratajczak, Allison Desveaux, Gérard Socié, Anne Janin

Paris, December 20th 2006

To the Editor, Biology and Bone Marrow Transplantation

Philippe Ratajczak, Ph.D.

Allison Desveaux

Gérard Socié, M.D., Ph.D.

Anne Janin, M.D., Ph.D.

Alveolar hemorrhage and acute graft versus host disease.

The very complete study of Majhail and al [1] on diffuse alveolar hemorrhage (DHA) and infection-associated alveolar hemorrhage (IAH) following hematopoietic stem cell transplantation (HSCT) highlights significant points: the overlap between DAH and IAH in a large series of transplanted patients, the better survival of patients with early-onset alveolar hemorrhage, the allogeneic donor source and severe acute graft versus host disease (GVHD) as risk factors independently associated with increased incidence of post-HSCT alveolar hemorrhage.

These thoroughly analyzed clinical data are in accordance with the experimental data we obtained in a murine model of allogeneic splenocytes transferred into immunodeficient mice [2]. This model, devoid of conditioning, offers the opportunity to study the cell and tissue lesions induced by the allogeneic reaction, without interference from radiotherapy sequels. We showed that endothelial cells of all organs, including lungs, were early targets of the allogeneic reaction, and that damaged endothelial cells underwent apoptotic death mediated by Fas ligation. In the mice lungs, endothelial damage led to alveolar hemorrhage, associated with lymphocytic bronchitis, a pathologic feature observed in patients with GVHD [3]. Further studies on human biopsies with allogeneic and autologous HSCT showed endothelial lesions and pericapillary hemorrhages linked to severe acute GVHD in upper digestive tract [4]. Another systematic pathological study of human biopsies showed the reduction of endothelial cell surface in the skin of patients with chronic GVHD [5]. Since lung biopsies are much more difficult and dangerous to perform than skin and duodenal biopsies, no systematic pathological study on human lung biopsies has been reported so far. The study of Majhail and al, as a previous report of pulmonary hemorrhage as a cause of death in patients with severe

acute GVHD [6] supports the fact that, as in the digestive tract, severe acute GVHD contributes to hemorrhage in patients' lungs through endothelial cell damage.

Sequential study in our experimental model showed that endothelial apoptosis is an early damage in the allogeneic reaction, and that all endothelial cells are not at once apoptotic. Therefore, alveolar hemorrhage is focal in early lesions (Figure 1a), limited, as we found in digestive tract of patients with GVHD, to the areas where endothelial damage has been severe enough to be associated with capillary basal lamina rupture (Figure 1c). Diffuse alveolar damage (Figure 1b) occurs later and for severe acute allogeneic reactions, induced in our model by transfer of a high number of allogeneic lymphocytes [2]. These experimental data are in accordance with one of the main points underlined by Majhail and al: the difficult distinction between DAH and IAH in HSCT recipients.

The endothelial damage linked to acute allogeneic reaction, if it takes place early in the course of the lung disease, may also contribute to explain the more favourable outcome of early-onset alveolar hemorrhage in this large series of HSCT recipients. Cell death through apoptosis, as observed in target cells of GVHD, does not induce an inflammatory reaction [7]. The vascular endothelium is composed of only one layer of endothelial cells, and apoptotic endothelial cells can be cleared by the blood flow [8, 9]. Therefore, endothelial cell repair can more rapidly and efficiently occur after endothelial apoptosis than after whole tissue damage linked to infectious disease. Experimental studies have shown that endothelial repair occurs either through local migration and proliferation of endothelial cells adjacent to the site of injury, or through homing and incorporation of bone marrow-derived endothelial progenitor cells on the site of endothelial injury [8, 9]. Although endothelial cell division, which may reach 50% of the cells in and around the injured sites after induced arterial denudation [10], might be active in GVHD patients, the role of bone marrow-derived cells has been recently emphasized. Endothelial cells of donor origin were found in two sequential series of

transbronchial biopsies of HSCT patients [11]. In skin biopsies we only found donor-derived endothelial cells in HSCT patients with GVHD, and the number of chimeric cells was linked to the severity of GVHD induced cell damage [12]. Particularly relevant to the GVHD-induced apoptotic damage is the recent in vitro demonstration that apoptotic bodies from endothelial cells enhance the number and initiate the differentiation of human endothelial progenitor cells in vitro [13].

As stated by Majhail, the current etiopathogenic paradigm for DAH is based on non transplantation DAH in systemic vasculitides and collagen vascular disease. Even on these DAH non related to transplantation, no pathological study of early events is available in humans. Therefore systematic studies of pure allogeneic reactions induced in animal models could help identifying the participation of acute GVHD in the alveolar hemorrhages following HSCT.

References

1. Majhail NS, Parks K, Defor TE et al.: Diffuse alveolar hemorrhage and infection-associated alveolar hemorrhage following hematopoietic stem cell transplantation: related and high-risk clinical syndromes, Biol Blood Marrow Transplant 2006, 12:1038-1046

2. Janin A, Deschaumes C, Daneshpouy M et al.: CD95 engagement induces disseminated endothelial cell apoptosis in vivo: immunopathologic implications, Blood 2002, 99:2940-2947

3. Yousem SA: The histological spectrum of pulmonary graft-versus-host disease in bone marrow transplant recipients, Hum Pathol 1995, 26:668-675

4. Ertault-Daneshpouy M, Leboeuf C, Lemann M et al.: Pericapillary hemorrhage as criterion of severe human digestive graft-versus-host disease, Blood 2004, 103:4681-4684

5. Biedermann BC, Sahner S, Gregor M et al.: Endothelial injury mediated by cytotoxic T lymphocytes and loss of microvessels in chronic graft versus host disease, Lancet 2002, 359:2078-2083

6. Wojno KJ, Vogelsang GB, Beschorner WE et al.: Pulmonary hemorrhage as a cause of death in allogeneic bone marrow recipients with severe acute graft-versus-host disease, Transplantation 1994, 57:88-92

7. Granville DJ, Carthy CM, Hunt DW et al.: Apoptosis: molecular aspects of cell death and disease, Lab Invest 1998, 78:893-913

8. Woywodt A, Bahlmann FH, De Groot K et al.: Circulating endothelial cells: life, death, detachment and repair of the endothelial cell layer, Nephrol Dial Transplant 2002, 17:1728-1730

9. Woywodt A, Haubitz M, Buchholz S et al.: Counting the cost: markers of endothelial damage in hematopoietic stem cell transplantation, Bone Marrow Transplant 2004, 34:1015-1023

10. Ingram DA, Caplice NM, Yoder MC: Unresolved questions, changing definitions, and novel paradigms for defining endothelial progenitor cells, Blood 2005, 106:1525-1531

11. Spencer H, Rampling D, Aurora P et al.: Transbronchial biopsies provide longitudinal evidence for epithelial chimerism in children following sex mismatched lung transplantation, Thorax 2005, 60:60-62

12. Murata H, Janin A, Leboeuf C et al.: Donor-derived cells and human graft-versus-host disease of the skin, Blood 2006,

13. Hristov M, Erl W, Linder S et al.: Apoptotic bodies from endothelial cells enhance the number and initiate the differentiation of human endothelial progenitor cells in vitro, Blood 2004, 104:2761-2766

Figure 1

a) Focal alveolar hemorrhage (arrows) in early lesions of allogenic reaction, b) diffuse alveolar damage in severe acute allogeneic reaction, and c) ultra-structural aspect of capillary basement membrane rupture (arrows).