Nonmyeloablative conditioning followed by hematopoietic cell allografting and donor lymphocyte infusions for patients with metastatic renal and breast cancer

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The feasibility and toxicity of allogeneic stem cell transplantation after nonmyeloablative conditioning including thiopeta, fludarabine, and cyclophosphamide has been investigated in 6 patients with breast cancer and 7 patients with renal cell cancer. The program included the use of escalating doses of donor lymphocyte infusions (DLI) and/or interferon alpha (IFNα) for patients showing no tumor response and no graft-versus-host disease (GVHD). Patients were at high risk of transplant-related mortality (TRM) because of age, advanced stage, and previous treatments. We observed a partial remission in 4 renal cancer and in 2 breast cancer patients (one at the molecular level in the bone marrow), occurring after cyclosporine withdrawal or after DLI and/or IFNα. All the responses were accompanied by the occurrence of acute GVHD. We conclude that reduced-intensity allogeneic stem cell transplantation is a feasible procedure in renal and breast cancer, and that the exploitation of graft-versus-tumor effect after DLI is a promising finding. (Blood. 2002;99:4234-4236)

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Results and discussion

All patients had a sustained myeloid and platelet engraftment (neutrophils ≥ 500/mL, median day 12, range 10-14; platelets ≥ 20,000/mL, median day 12, range 8-16 days). On day ±60, bone marrow chimerism was more than or equal to 80% donor in 12 of 13 patients; peripheral blood (PB) myeloid engraftment was more than or equal to 80% in 10 of 11 patients, and PB lymphoid chimerism was more than or equal to 80% in 9 of 11 evaluable patients.

No early TRM was observed during the first 100 days; one patient died of late TRM for lung and brain aspergillus infection. Acute GVHD grades II-III developed in 8 patients (3 after DLI) a median of 95 days after transplantation (range, 12-208 days). Of these 8 patients, 7 progressed to chronic GVHD: 2 limited and 5 extensive forms. The median follow-up was 417 days (range, 120-782). We observed 2 partial responses (patients no. 3 and no. 6): one after a single-dose DLI, the other after 2 infusions followed by CSA withdrawal. DLIs were given to 7 patients progressing after allografting, and 3 achieved a partial remission. All responses occurred after the development of acute GVHD, and with full donor T-cell chimerism.

There were 3 of 7 RCC patients who progressed soon after the transplantation (median time, 61 days). There were 4 patients who responded after CSA withdrawal; patient no. 7 relapsed but eventually responded again to DLIs plus IFNα (Figure 1A). The other 2 RCC patients had stable disease, and patient no. 11 (papillary RCC) died of progressive disease 10 days after the DLI. Patient no. 3 achieved a partial remission according to RECIST criteria (12). No complete responses were observed; 4 patients responded following CSA withdrawal. DLIs were given to 7 patients progressing after allografting, and 3 achieved a partial remission. All responses occurred after the development of acute GVHD, and with full donor T-cell chimerism.
We and others have previously shown that RT-PCR for maspin and mammaglobin is a sensitive and specific assay for detecting occult BC cells. This finding suggests a GVT effect at the marrow level.

Our data confirm the existence of a graft-versus-RCC effect demonstrated by Childs et al. There were 4 of 6 patients with renal clear cell carcinoma and a sufficient follow-up who achieved a PR after withdrawal of CSA or after DLI plus IFNα. Clinical evidence of graft-versus-BC effect has been reported in a limited number of patients (2/10) by Ueno et al, and in one anecdotal case by Eibl et al. However, the study by Ueno et al was different from ours in that it included patients without progressive disease, adopted a myeloablative conditioning regimen with demonstrated antitumor activity, and performed DLI in only one case without response. The dose of T cells to induce a clinical response may vary in different malignancies: Lokhorst et al have shown that effective DLI doses for relapsed multiple myeloma are higher than those used for chronic myeloid leukemia. Whether this principle applies to solid tumors, and in particular to BC, is still uncertain. Further, the utilization of specific T-cell subsets, the optimal time interval from allograft to DLI, and the schedule of IFNα administration to enhance a GVT effect remain to be determined.

**References**

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