Biol Blood Marrow Transplant 22 (2016) 676–681

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Long-Term Follow-Up of Allogeneic Hematopoietic Stem Cell Transplantation for Solid Cancer

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Article history:
Received 27 October 2015
Accepted 19 December 2015

Key Words:
Allogeneic hematopoietic stem cell transplantation
Renal carcinoma
Cholangiocarcinoma
Colon carcinoma
Pancreatic adenocarcinoma

A B S T R A C T

We wanted to determine whether allogeneic hematopoietic stem cell transplantation (HSCT) may result in long-term survival in patients with solid cancer. HSCT was performed in 61 patients with solid cancer: metastatic renal carcinoma (n = 22), cholangiocarcinoma (n = 17), colon carcinoma (n = 15), prostate cancer (n = 3), pancreatic adenocarcinoma (n = 3), or breast cancer (n = 1). Liver transplantation was performed for tumor debulking in 18 patients. Median age was 56 years (range, 28 to 77). Donors were either HLA-identical siblings (n = 29) or unrelated (n = 32). Conditioning was nonmyeloablative (n = 23), reduced (n = 36), or myeloablative (n = 2). Graft failure occurred in 13 patients (21%). The cumulative incidence of acute graft-versus-host disease (GVHD) of grades II to IV was 47%, and that of chronic GVHD was 32%. Treatment-related mortality was 21%. At 5 years cancer-related mortality was 63%. Currently, 6 patients are alive, 2 with renal cell carcinoma, 1 with cholangiocarcinoma, and 3 with pancreatic carcinoma. Eight-year survival was 12%. Risk factors for mortality were nonmyeloablative conditioning (HR, 2.95; $P < .001$), absence of chronic GVHD (HR, 3.57; $P < .001$), acute GVHD of grades II to IV (HR, 2.90; $P = .002$), and HLA-identical transplant (HR, 5.00; $P = .03$). With none of these risk factors, survival at 6 years was 50% (n = 6). Long-term survival can be achieved in some patients with solid cancer after HSCT.

INTRODUCTION

It is evident that the immune system may control cancer [1,2]. After allogeneic hematopoietic stem cell transplantation (HSCT), acute and chronic graft-versus-host disease (GVHD) has been found to contribute to and maintain an antileukemic effect. This so-called graft-versus-leukemia effect is thought to be mainly induced by alloreactive T cells, and it may be abrogated by T cell depletion of the graft [3]. The anticancer effect of HSCT has mainly been used in patients with leukemia and other hematologic malignancies [1,2].

A graft-versus-tumor effect has been found in breast cancer [4]. Childs et al. [5] have shown a graft-versus-tumor effect in metastatic renal cell carcinoma. Subsequently, several studies have shown that HSCT is an effective treatment for metastatic renal carcinoma [6-9]. The finding of a graft-versus-breast cancer effect and the work of Childs et al. on metastatic renal cell carcinoma have stimulated several centers to use HSCT to induce an anticancer effect in metastatic colon carcinoma, ovarian carcinoma, advanced pancreatic carcinoma, prostate cancer, liver cancer, and neuroblastoma [2,9-14].

Most patients with solid cancer who are referred for HSCT have advanced disease, and the major problem is death due to progression of the cancer. The high expectations for HSCT have not been fulfilled. New drugs have been developed, for example, those targeting tyrosine kinase or associated receptors and antibodies to epidermal growth factor receptor (among other proteins) [15,16]. The interest in referring patients with advanced solid tumors for HSCT has, however, declined.

Here we describe our experience of HSCT in 61 patients with solid cancer, with a median follow-up of 8 years, with

Financial disclosure: See Acknowledgments on page 681.

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http://dx.doi.org/10.1016/j.bbmt.2015.12.017
1083-8791/

the longest survivor 12 years after HSCT. Six of these patients are still alive.

METHODS

Patients

Between August 1999 and August 2012, 22 patients with metastatic renal carcinoma, 17 with cholangiocarcinoma, 15 with colon cancer, 3 with prostate cancer, 3 with pancreatic cancer, and 1 with breast cancer were treated with HSCT. All patients had been considered to have tumors that were incurable with any conventional therapy (Table 1). All but 2 patients underwent debulking of the primary tumor, and in 14 patients surgical reduction of metastases was also performed. In 6 patients debulking was done using radiofrequency ablation. All patients with hepatic cholangiocarcinoma and 1 patient with colon carcinoma (with liver metastases) underwent orthotopic liver transplantation as debulking before HSCT [14,17]. Three patients with pancreatic cancer underwent Whipple surgery with radical intent. Thirty-one patients had been given additional therapy previously, such as cytotoxic drugs, irradiation, or immunotherapy. All 3 patients with prostate cancer had been treated with androgen deprivation therapy before HSCT. Patient and donor characteristics are given in Table 2. The studies were approved by the Research Ethics Committee of Karolinska Institutet (88/96, 69/99, 385/99, and 2006/858-314).

Donors and Stem Cells

HLA typing with high-resolution PCR was used for HLA class I and II. HLA-identical sibling donors were given priority, and these were found for 29 patients. An HLA-matched unrelated donor (MUD) was identified for 27 patients. A graft from an HLA-A, -B, or -DR mismatched unrelated donor was given to 5 patients. Two of those received major HLA-mismatched marrow and a liver graft from the same cadaveric donor [17]. Most patients were given peripheral blood stem cells mobilized with granulocyte colony-stimulating factor stimulation of the donor (10 μg/kg/day, Neupogen; Amgen, Stockholm, Sweden) [18]. Four patients were given bone marrow grafts.

Conditioning

Nonmyeloablative conditioning consisted of fludarabine, 30 mg/m^2/day for 3 consecutive days, in patients with an HLA-identical sibling donor and for 5 days in those with a MUD, followed by 2 Gy of total body irradiation ($n = 23$) [19]. Because of the high rate of graft failure using this protocol [20], we switched to a protocol with fludarabine for 5 days followed by cyclophosphamide, 30 mg/kg/day for 2 days, which was used in 36 patients [21]. The 2 patients who received cadaveric donor grafts were given myeloablative conditioning consisting of cyclophosphamide, 120 mg/kg, and 7.5 Gy total body irradiation [17].

GVHD Prophylaxis and Treatment

Cyclosporine was given to almost all patients for at least 3 months. Cyclosporine dose ranged between 3 and 12 mg/kg/day, divided into 2 doses, to achieve a trough level of 100 ng/mL in patients with a sibling donor and between 200 and 300 ng/mL in patients with a MUD [22]. Initially, 19 patients also received mycophenolate mofetil, .5 to 1 g twice a day for 1 to 2 months [19]. Because of a high rate of graft failure and gastrointestinal toxicity with this regimen, this was replaced with 4 doses of methotrexate [20]. In the 17 patients with liver cancer who underwent debulking with a liver transplant, cyclosporine was replaced with tacrolimus to achieve trough levels of 8 to 10 ng/mL. The 2 patients who received cadaveric bone marrow from the liver graft donor were given T cell–depleted recipient and autologous bone marrow grafts [17]. All patients with an unrelated donor were treated with antithymocyte globulin (SangStat, Lyon, France) at a dose of 8 to 10 mg/kg [23]. Initial treatment of grade I acute GVHD was prednisolone, 2 mg/kg/day [22]. Patients who did not respond to prednisolone were treated with mesenchymal stromal cells (MSCs) or decidual stromal cells [24].

Supportive Care

Prophylaxis against infections included ciprofloxacin p.o., fluconazole p.o., nystatin p.o., acyclovir p.o., and cotrimoxazole according to our HSCT protocol [22]. Patients were treated in reversed isolation in the hospital or at home during the pancytopenic phase after HSCT [25]. Supportive care has been described previously in detail [22,25].

Donor Lymphocyte Infusions

Donor lymphocyte infusions (DLIs) were given in escalating doses (1, 5, 10, and 100×10^6 CD3$^+$ cells/kg), starting 3 to 4 months after HSCT, if the immunosuppressive therapy had been discontinued and in the absence of severe GVHD [26].

Table 1
Location of Malignancy, Grade/Stage Differentiation, and Number of Metastases

Location of Malignancy	Differentiation Grade/Stage	Metastases, Number of Sites
Renal	Adenocarcinoma	
R1	Low	1
R2	High	2
R3	Mid-high	3
R4	Low	2
R5	Mid-high	3
R6	Mid-high	3
R7	Mid-high	3
R8	High	1
R9	Mid-high	2
R10	Mid-high	2
R11	Mid-high	3
R12	Low	3
R13	Low	2
R14	Low	0
R15	Low	2
R16	Necrotic tumor	1
R17	Mid-high	2
R18	Low	2
R19	High	1
R20	Low	2
R21	Low	0
R22	Sarcoma	1
Prostate	Adenocarcinoma	
P1	Gleason 4 + 4	1
P2	Gleason 3 + 3	0
P3	Gleason 4 + 5	1
Pancreas	Ductal adenocarcinoma	
PD1	T3N1V1Pn1	0
PD2	T3N0V1Pn1	0
PD3	T3N1V1Pn1	0
Breast	Ductal adenocarcinoma	
B1	Low	2
Colon	Adenocarcinoma	
C1	Mid-high	2
C2	Mid-low	4
C3	Mid-high	2
C4	Mid-high	3
C5	Mid-high	2
C6	Mid-high	2
C7	Mid-high	3
C8	Mid-high	3
C9	Low	1
C10	Mid-high	1
C11	Mid-high	2
C12	Mid-high	2
C13	Mid-high	3
C14	Mid-high	2
C15	Mid-high	1
Liver	HCC/ cholangiocarcinoma	
L1	Mid-high	2
L2	Mid-high	0
L3	Mid-high	1
L4	Mid-low	0
L5	Mid-high	0
L6	High	1
L7	Mid-high	2
L8	Mid-high	0
L9	Mid-high	2
L10	Mid-high	0
L11	Mid-high	1
L12	Low	0
L13	High	0
L14	Klatskin	0
L15	Mid-high	0
L16	Mid-high	1
L17	Mid-high	1

HCC indicates hepatic cholangiocarcinoma.