138 INVITED

Results in renal cell cancer: induction of graft-vs-tumor effects in renal cell carcinoma and other tumors solid tumors following allogeneic stem cell transplantation

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Since 1998, we and others have conducted pilot trials investigating for graft-vs-tumor (GVT) effects following nonmyeloablative allogeneic stem cell transplantation (NST) in patients with metastatic renal cell carcinoma and other treatment refractory solid tumors. At the NHLBI, patients have been conditioned with cyclophosphamide (60 mg/kg × 2) and fludarabine (25 mg/m^2 × 5) then transplanted with a G-CSF mobilized blood stem cell allograft from their HLA identical or single antigen mismatched related donor. Cyclosporine (CSA) alone or in combination with mycophenolic acid (MMF) has been used as GVHD prophylaxis and withdrawn early in patients with mixed T-cell chimerism or disease progression.

Renal cell carcinoma was quickly identified as being a target for GVT effect. Ten of the first 19 and subsequently 26 of the first 73 (36%) patients had regression of metastatic disease compatible with a GVT effect. Regression of metastatic tumor was 1) Delayed a median of 5 months (range 2–13 months) following transplant 2) Usually followed CSA/MMF tapering or withdrawal 3) Occurred after a donor lymphocyte infusion (DLI) in 5 patients 4) Was favorably associated with a history of GVHD 5) Typically did not occur until T-cell chimerism had transitioned from mixed to predominantly donor. Five patients who had had previously failed interferon alpha treatment had a disease response when they were re-treated with interferon alpha post-transplant. Additionally, in the non-responding cohort, a mixed response was observed in 6 (11%) patients. To date, disease regression has only been observed in patients having tumors with clear cell histology. The first patient transplanted with metastatic RCC remains in complete remission more than 7 years since undergoing treatment. Six patients (8%) died from transplant related causes. Acute grade II–IV graft-vs-host disease has been the major toxicity associated with the procedure occurring in approximately 35% of patients and has been fatal in 5 cases. We observed no benefit of adding MMF to CSA for GVHD prophylaxis following NST; Kaplan-Meier estimate of incidence of grade II–IV acute GVHD was 58% in the group receiving CSA alone (95%CI: 46–70%) vs 57% in group receiving CSA + MMF (95%CI: 45–69%; p value = NS). The effect of using CSA in conjunction with mini-dose methotrexate (5 mg/m^2 days +1, +3, +6) as GVHD prophylaxis is currently under investigation.

The observation of GVT effects in RCC led us and others to initiate similar trials of nonmyeloablative allogeneic transplantation for patients with a variety of different treatment refractory solid tumors. Although these trials are ongoing, evidence for a GVT effect in a patients with metastatic colon carcinoma, ovarian carcinoma, pancreatic carcinoma and breast carcinoma following NST has recently been reported by a number of investigators.

The immune mediators contributing to the GVT effect in RCC continue to be investigated. In-vitro data obtained from the analysis of patient's lymphocytes during disease regression indicate that anti-tumor immune responses may be mediated through both tumor specific and/or "allo-reactive" (non-tumor restricted) donor T-cell responses. We have successfully generated donor CD8+ T-cell clones from lymphocytes obtained from responding patients that have direct cytotoxicity against the patient's RCC cells. Using C-DNA expression cloning, the target antigen of an HLA-A 11 restricted RCC specific T-cell clone isolated from a patient at the time of tumor regression (donor in origin) is currently being categorized. Interestingly, in one patient who had disease regression associated with acute GVHD, we were able expand CD8+ T-cell clones which recognized both autologous EBV transformed B cells and patient RCC cells, strongly implicating minor histocompatibility antigens as being the target for a GVT effect in this patient.

These studies have provided proof of concept of the graft-vs-solid tumor effect and laid the foundation for the development of tumor targeted allogeneic approaches. Future investigations will focus on limiting the toxicity related to the procedure, and directing the immune response specifically to the tumor. One of the major challenges with these approaches will be to obtain blockade of GVHD without compromising GVT effects.

139 INVITED

Non-myeloablative transplantation in solid tumors-results in other solid tumors

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Non-myeloablative transplantation in solid tumors is a hot topic attracting transplanters in an attempt to treat refractory solid tumors such as renal cell, breast and colon cancer. Approximately 300 hundreds patients with renal cancer have been treated with this strategy during last 5 years. Today, in my talk, I will focus on solid tumors other than renal cell cancer such as breast, colon, pancreatic cancer and sarcomas. To describe the efficacy of allogeneic hematopoietic cell transplantation for metastatic breast cancer, we reviewed registry data from 16 centers participating in the Center for International Blood and Marrow Transplant Research and the European Group for Blood and Marrow Transplantation between 1992 and 2000. Probabilities of transplant-related mortality (TRM), graft-vs-host disease (GVHD), disease relapse or progression, progression-free survival, and overall survival were determined. Seventy-five patients were identified from the registries; median age at transplant was 41 years (range, 25–60) and the median follow-up time for survivors was 25 months (range, 3–64). Thirty-nine patients (52%) received myeloablative conditioning regimens and 36 (48%) were given reduced-intensity conditioning (RIC) regimens. Patient characteristics were similar between the two groups except that more patients in the RIC group (72%) had low performance status than did those in the myeloablative group (26%). More patients in the myeloablative group had acute GVHD (46% vs 33% in the RIC group) at 100 days, chronic GVHD at 1 year (39% vs 8% in the RIC group), and 100-day TRM (26% vs 7% in the RIC group). Overall response rates (complete or partial response) were 31% for the myeloablative group and 29% for the RIC group. Nine of 38 patients (24%) who underwent immune manipulation after transplant showed disease control, providing direct evidence of a graft-vs-tumor effect. Further, multivariate analysis showed that the presence of acute GVHD after an RIC regimen reduced the risk of disease relapse or progression but did not affect progression-free survival. The presence of disease control in association with acute GVHD suggests the existence of a graft-vs-tumor effect in heavily pretreated metastatic breast cancer patients. GVT effect in colon cancer (Zetterquist et al. 2001) was also shown with necrosis of tumor. Therefore, EBMT STWP started to evaluate the GVT effect in colon cancer with a retrospective survey. Similarly, GVT effect in pancreatic cancer (Omuro Y et al. 2003) was reported. According to the EBMT Survey 25 patients with soft tissue sarcoma were treated with allogeneic transplantation. Sixteen of 25 received PBSC and 9 received marrow. Nine of 25 patients received NMSCT and 12 received an intensive conditioning. Eleven of 25 patients had progressive disease, 8 had CR and 3 had primary refractory disease at transplant. Thirty percent of patients had AGVHD with a median survival of 12 months for patients in CR and PR. This survey is currently ongoing. In Summary, There is a GVT effect in patients with various solid tumors treated with NMSCT. Further studies are needed in order to optimal explotation of this effect and I think it would be the best to target those patients with metastatic solid tumors in the early period of their diseases.

Scientific Symposium
Treating oesophageal cancer

140 INVITED

Epidemiology of oesophageal cancer

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The epidemiology of oesophageal cancer has been changing in many countries over recent decades. The incidence of the disease varies substantially worldwide, with high rates reported especially in China, central Asia, parts of north-west Europe, east Africa, and among black people in South Africa and the United States of America.

Rates of oesophageal cancer are generally increasing or stable across European countries. A striking increase in adenocarcinoma of the oesophagus has been reported from many countries. While this may be explained, in part, by shifts in classification and/or diagnostic practice and/or the proportion of unspecified tumours, it probably also represents a genuine increase in risk associated with historic changes in prevalence of some established risk factors.

Overall, oesophageal cancer is more common in males. The disease is uncommon below the age of 40 years, but thereafter risk increases quite steeply to peak in the elderly. Squamous cell carcinoma is more common in black people and in persons of lower socio-economic status, whereas adenocarcinoma is more common in white people.

The main established risk factors for squamous cell carcinoma of the oesophagus are alcohol, tobacco, and poor diet. Risk factors for adenocarcinoma are gastro-oesophageal reflux disease (GORD), obesity, Barrett's oesophagus, tobacco, and poor diet. Understanding the epidemiology, aetiology, and natural history of oesophageal cancer is key to developing rational strategies for primary prevention and screening of high risk populations.