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The Effect of Smoking on Allogeneic Transplant Outcomes

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Using the Center for Internaitonal Blood and Marrow Transplant Research (CIBMTR) data, we compared the transplant outcomes of patients with chronic myelogenous leukemia (CML) who were nonsmokers (NS) and past or current smokers (PCS). There were 2193 NS and 625 PCS who received matched sibling and unrelated donor allografts for CML in first chronic phase. We looked for dose effects and identified low and high dose smoking groups (>10 pack years, >1 pack per day). Outcomes were adjusted for known prognostic variables including the European Group for Blood and Marrow Transplant (EBMT) risk score. In multivariate analyses of sibling allograft recipients, relapse risk (RR) was higher (RR = 1.67, $P = .003$) in smokers than NS, but the dose effects were not consistent. High-dose smokers experienced a 50% treatment-related mortality (TRM) versus 28% in the NS group at 5 years on univariate analysis, and the RR was 1.57 ($P = .005$) on multivariate analysis. Overall survival (OS) at 5 years was 68% in NS versus 62% in the low-dose smoking group versus 50% in the high-dose smoking group ($P < .001$). Smoking did not significantly affect outcomes in unrelated donor recipients, but numbers were smaller. High-dose smoking is associated with a reduction in OS in patients having sibling allografts for CML. A prospective study with detailed demographic, pulmonary function, and quality-of-life data would improve our understanding of this issue.

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INTRODUCTION

Allogeneic stem cell transplantation is widely used to cure patients with leukemia and other hematologic conditions. Various biologic factors influence the transplant outcome of patients with chronic myelogenous leukemia (CML). These include patient age [1] (Center for International Blood and Marrow Transplant Research [CIBMTR], unpublished data), performance status at transplant [2], and body mass index [1]. Pretransplant pulmonary function may also affect overall transplant outcome and posttransplant respiratory complications [3,4]. One of the major causes of pretransplant respiratory abnormalities is cigarette smoking. Depending on the population studied, between 20% and 50% of adult allogeneic transplant candidates have a current smoking history, and many additional patients have a past smoking history. Smoking, as well as affecting pulmonary function, can influence the risk of coronary artery disease [5], and is an important cause of lung cancer (which may be increased after allogeneic transplantation) [6]. Smokers are known to have different demographics than nonsmokers (NS). They are more likely to be male, of a lower socioeconomic status [7,8], and have a higher alcohol intake [9]. In studies of the effect of smoking on health outcomes, it is possible that these associations of smoking may affect the outcomes.

No large-scale studies address the effect of smoking on transplant outcome. The CIBMTR database,

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which includes data on smoking history, is ideal for this purpose. We hypothesized that a smoking history would significantly reduce the chance of a successful transplant outcome by increasing treatment-related mortality (TRM), primarily through pulmonary complications, including infection. Relapse incidence was also studied because physicians may have altered conditioning in patients who smoke. Smoking may affect the incidence of secondary malignancies, but this study was not designed to address this issue.

We elected to study patients with CML in first chronic phase (CP1), because we hypothesized that examining the effect of smoking in a chemotherapy naïve population would "isolate" the effect of smoking. Smoking might make pulmonary complications more likely after pretransplant chemotherapy, but we wished to study the effect of smoking on transplant alone. This focus on CML also eliminated a potential source of patient heterogeneity, and the prognostic factors affecting the transplant outcome of CML patients are well described [10]. We analyzed sibling and unrelated donor transplants separately, as the latter has a greater TRM and may have received higher doses of total body irradiation (TBI).

There are numerous practical implications of performing this study. Transplant teams will be able to inform better patients who smoke about the chances of a successful outcome. The study may generate information that enables transplanters to modify conditioning regimens to increase the chance of a successful outcome. Finally, when the causes of treatment failure are determined, transplanters may be able to direct their supportive care efforts to preventing specific problems.

PATIENT SELECTION AND INCLUSION CRITERIA

Patient data for this study were obtained from the CIBMTR. More than 500 participating centers register consecutive allogeneic transplants to CIBMTR. Detailed demographic and clinical data are collected on a sample of registered patients. Compliance is monitored by on-site audits. Computerized error checks, physician reviews of submitted data, and on-site audits of centers ensure the quality of data.

This study included all patients between 1990 and 2004, aged 18 years and above, who received HLA-identical sibling or matched unrelated donor (MUD) allogeneic transplants for CML in CP1 for whom a smoking history was known. Patients received busulphan (Bu) and cyclophosphamide (Cy) or TBI and Cy for conditioning. Graft type was restricted to bone marrow (BM) or peripheral blood (PB). Graft-versus-host disease (GVHD) prophylaxis was restricted to cyclosporine (CsA) and methotrexate (MTX), tacrolimus and MTX, T cell depletion, or CsA and other immunosuppressive agents. Patients who received low-dose oral Bu prior to transplant were excluded.

The number of patients with CML in CP1 aged >18 years who had allografts reported to the CIBMTR between 1990 and 2004 was 5461. A total of 5022 patients received a sibling or MUD allograft of BM or PB. We only included the 4409 receiving Cy/TBI or Bu/Cy conditioning and excluded the patients who had received prior low-dose Bu, leaving 3880 patients. We confined our study to 3793 patients with specific types of GVHD prophylaxis (defined before). Finally, we had quantitative smoking information for 2818 of these patients.

Smoking Data

Patients were categorized as NS or past or current smokers (PCS) based on self-reported responses extracted from medical notes by data managers completing the CIBMTR forms. The questions, which asked about smoking history, varied slightly in 1989, 1995, and 2002. However, all questionnaire versions enquired about duration and number of cigarettes per day. The quantitative data regarded number of years smoked and amount per day (<1 pack, 1 pack and >1 pack) enabling us to compare the major outcomes in these groups and look for a dose effect. In this study PCS are termed "smokers." We divided smokers into 2 "doses": high-dose smokers had accumulated >10 pack years and smoked >1 pack per day, and low-dose smokers had ≤10 pack years or ≤1 pack per day.

Statistical Methods

Patient-, disease-, and treatment-related variables for patients in the 3 smoking groups were compared using chi-square test for categoric variables and the Kruskal-Wallis test for continuous variables. *P*-values for pair-wise comparison were adjusted using Bonferroni correction.

The primary endpoints were relapse, TRM, disease-free survival (DFS), and overall survival (OS). The event relapse was defined as occurrence of CML (clinical and/or cytogenetic) posttransplant. TRM was defined as death within 28 days posttransplant or death without CML relapse. Smoking may affect the incidence of fungal infection, but because our data does not allow us to verify this diagnosis, this was not an endpoint of the study.

Probabilities of TRM and relapse were calculated using the cumulative incidence function method [11]. Treatment-related death and relapse were the competing events. Data on patients without either competing event were censored at last follow-up. For analyses of survival, death from any cause was considered an event and surviving patients were censored at last follow-up.