RAPID COMMUNICATION

Increased Incidence of Solid Malignant Tumors After Bone Marrow Transplantation for Severe Aplastic Anemia


From May 1980 to December 1989, 107 consecutive patients with non-constitutional severe aplastic anemia underwent bone marrow transplantation at our institution using cyclophosphamide and thoraco-abdominal irradiation as conditioning regimen. During the same period, 40 patients with Fanconi anemia were also grafted after a similar conditioning, giving a total series of 147 patients. With a mean follow-up of 64 months, four male patients developed a solid malignant tumor, a number that leads to an 8-year cumulative incidence rate of 22% (eg, relative risk to general population = 41, P < .001). These results should be considered as a warning to clinicians who follow these successfully grafted long-term patients.

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LOGENEIC BONE MARROW transplantation (BMT) has been an increasingly world-wide used therapeutic modality for hematologic malignancies and other non-malignant hematologic disorders.

Secondary malignancies have been reported after chemotherapy, radiotherapy, and tumors, especially of epidermal tissues and lymphatic system, have been observed after solid organ transplantation. Furthermore, studies in canine and non-human primate radiation chimeras have shown a significantly increased risk of developing secondary malignancy.

Therefore, one would expect that human marrow transplant recipients treated with high dose chemotherapy and/or radiotherapy and postgrafting immunosuppression are at high risk of developing secondary malignancies. However, only few reports have depicted this special issue, so far.

 PATIENTS AND METHODS

We recently updated (Blood, submitted) our experience using cyclophosphamide (150 mg/kg)-thoraco-abdominal irradiation (TAI) (6 Gy) as conditioning regimen before BMT for severe aplastic anemia (SAA). We used large-field irradiation within conditioning regimen because it was shown to reduce the incidence of graft rejection. From May 1980 to December 1989, 107 consecutive patients with an acquired SAA received this regimen before BMT with an HLA-identical sibling donor. Graft-versus-host disease (GVHD) prophylaxis consisted in methotrexate (MTX) or cyclosporine A (CSA) or the association. In addition to these 107 patients, 40 patients with Fanconi anemia were grafted from November 1976 to July 1990; all but five received a modified conditioning regimen including cyclophosphamide (20 mg/kg)-TAI (5 Gy), and CSA for GVHD prophylaxis.

Mean follow-up of these 147 patients (males 87, females 60) was 64 months (range, 3 to 342), and mean follow-up from BMT to last examination was 36 months (range, 1 to 134). Mean age at diagnosis was 17 years (range, 5 to 46).

The time at risk for secondary solid tumor was computed from the date of BMT to the date of solid tumor occurrence, the date of last examination, or October 1, 1990, whichever came first. The excess of solid tumor was calculated as the ratio of observed (O) to expected (E) numbers from the French general population. The O/E ratio was computed using a cancer incidence rate specific for age, sex, and calendar year that has been published by the Bas-Rhin tumor registry in France. The confidence limits (CL) of O/E ratio were obtained by assuming a Poisson distribution for the observed numbers. A one-sided test was used to test the equality of O and E (O/E > 1 to be significant).

RESULTS

Four male patients developed a solid tumor, all within the radiation field. Main clinical parameters of these four patients are summarized in Table 1. Three patients were grafted for SAA and one patient for Fanconi anemia. Median age at the time of BMT was 16 years (range, 6 to 24), and median elapsed time from BMT to solid tumor was 7 years. Of the four malignant tumors, three were epidermoid carcinomas (patients unique patient number [UPN] 52, 71, and 83). The fourth one (patient UPN 97) was a mucoepidermoid carcinoma of the parotid gland. All four patients were treated by surgery and/or radiotherapy for their malignancies and three of four are alive with a median follow-up of less than 1 year.

Overall, the O/E ratio was 41 (95% CL: 10.9, 102; P < .001) for a total number of 446 person-years at risk. The O/E ratio was 80 in males (95% CL: 22, 205; P < .001). The 8-year cumulative incidence rate was 22% (standard error 11%) overall (Fig. 1).

Among the factors tested were age, sex, previous specific immunosuppressive therapy (n = 53), type of acute GVHD prophylaxis (n = 147), acute GVHD treatment (n = 98), occurrence of chronic GVHD (n = 67) and its treatment; none correlated with an increased risk of secondary solid tumor.

DISCUSSION

Late occurrence of solid tumors after BMT has rarely been reported. To our knowledge, only three groups have published such a long-term complication after BMT. It is noteworthy that only five other secondary solid tumor

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Two of those five patients with radiation-containing conditioning regimen, while the three others had only cyclophosphamide. In a recent report, Storb et al specifically analysed the risk of secondary solid malignant tumor in patients transplanted for SAA at Seattle. They report a 15-year cumulative incidence rate of 6%, which can be considered not different with that reported in the present series, ie, 22%, given the wide standard error. Besides previous chronic GVHD, which accounted for two of our patients with secondary solid malignant tumor as compared with four of four patients from Seattle, the main difference that might explain the high incidence rate reported is the systematic use of irradiation within the conditioning regimen in our patients. Whether the irradiation can totally explain the difference observed remains unsolved.

As previously emphasized, two of our four patients had oral chronic GVHD that may predispose to squamous carcinoma as in oral lichen planus. In addition, none of our patients were smokers nor drinkers. Obviously, with so limited numbers of patients at risk and so few patients developing a secondary solid malignant tumor, the search for risk factors is illusive.

More accurate assessment of incidence risk of solid tumor and risk factors will ideally come in the future from multi-institutional study. However, one of our major goals for the next few years will be to carefully study the late effects after BMT because, with improvement of long-term results, the number of patients at risk will increase.

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Increased incidence of solid malignant tumors after bone marrow transplantation for severe aplastic anemia [see comments]

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