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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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.

Table 1. Characteristics of Patients Who Secondarily Developed a Solid Malignant Tumor

<table>
<thead>
<tr>
<th>UPN</th>
<th>Diagnosis</th>
<th>Age/Sex</th>
<th>Previous IS</th>
<th>GVHD Prophylaxis</th>
<th>Extensive Chronic GVHD</th>
<th>Elapsed Time From BMT to Solid Tumor (mo)</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>52</td>
<td>SAA</td>
<td>24/M</td>
<td>ATG</td>
<td>CSA</td>
<td>Yes</td>
<td>64</td>
<td>Oral cavity</td>
</tr>
<tr>
<td>71</td>
<td>Fanconi anemia</td>
<td>6/M</td>
<td>No</td>
<td>CSA</td>
<td>No</td>
<td>74</td>
<td>Tongue</td>
</tr>
<tr>
<td>97</td>
<td>SAA</td>
<td>21/M</td>
<td>No</td>
<td>MTX</td>
<td>No</td>
<td>94</td>
<td>Parotid</td>
</tr>
<tr>
<td>83</td>
<td>SAA</td>
<td>12/M</td>
<td>No</td>
<td>MTX</td>
<td>Yes</td>
<td>95</td>
<td>Lip</td>
</tr>
</tbody>
</table>

Age denotes age at BMT, in years.

Abbreviations: IS, immunosuppressive therapy; ATG, antithymocyte globulin.

Fig. 1. Eight-year cumulative incidence rate of solid tumors after BMT for severe aplastic anemia or Fanconi anemia is 22% (standard error, 11%).


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

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