Second Malignancies after Allogeneic Stem Cell Transplantation with Reduced-Intensity Conditioning: Is the Incidence Reduced?

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Allogeneic hematopoietic stem-cell transplantation (SCT) is a potentially curative therapy for patients with a variety of malignant and nonmalignant hematological disorders. Over the last decades, substantial improvement has been achieved in SCT outcomes [1]. A larger proportion of SCT recipients are now long-term survivors and more attention is given to issues of quality of life and late complications. Second malignancies are a rare but well-defined late complication after allogeneic SCT with myeloablative conditioning (MAC), accounting for 5% to 10% of late deaths [2-6]. The incidence is gradually increasing after SCT, with no apparent plateau. The Center for International Blood and Marrow Transplant Research and the Fred Hutchinson Cancer Research Center conducted the largest analysis to date of second malignancies among 28,874 SCT recipients [2]. Second malignancies were observed in 189 patients, with a cumulative incidence of 1.0% at 10 years, 2.2% at 15 years, and 3.3% at 20 years. This rate was 2.1 higher than expected in a matched general population. The majority of patients in this analysis were given total body irradiation (TBI) during conditioning. Significantly elevated risks were observed for tumors of the oral cavity, liver, central nervous system, thyroid, bone, soft tissues, and melanoma of the skin. In a follow-up report, Majhail et al. studied 4318 patients with acute myelogenous leukemia (AML) and chronic myelogenous leukemia who were given allogeneic SCT with chemotherapy-based MAC consisting of busulfan and cyclophosphamide [3]. Sixty-six patients had a second malignancy, with a 10-year cumulative incidence of 1.2% in AML and 2.4% in chronic myelogenous leukemia, 1.4 times higher than expected in the general population. Significantly elevated risks were observed for tumors of the oral cavity, esophagus, lung, soft tissue, and brain. More recently, Atsuta et al. reported on 269 second malignancies among 17,545 Japanese SCT recipients, with a cumulative incidence 1.7% at 10 years, which was 1.8 more than a matched general population [6]. Risks were higher for oral cavity, esophageal, colon, skin, and brain cancers. Thus, despite regional and genetic differences in cancer incidence and sites, the impact of SCT on second cancer was similar in the various studies. Collectively, TBI was recognized as a major risk factor for nonsquamous cell cancers, especially when administered at younger age (<30 years) [2]. Chronic GVHD was a risk factor for squamous cell cancers, especially of the oral cavity. Advanced age was also a major risk factor for the occurrence of second malignancies.

The pathogenesis of second malignancies after allogeneic SCT is multifactorial. Radiation and chemotherapy exposure can induce breaks in the DNA double strand, resulting in gene mutations, deletions, translocations, and genomic instability conferred by loss of DNA repair [7]. Genomic alterations in mucosal epithelium, as evidenced by microsatellite instability, are common, including in tissues affected by graft-versus-host disease (GVHD), and may contribute to second malignancies [8]. Oncogenic viruses in the context of prolonged immune suppression may also take part in the pathogenesis.

Reduced-intensity conditioning (RIC) has been widely introduced over the last 15 years to allow SCT in older or medically infirm patients who are not eligible for standard MAC. RIC has been able to markedly expand the eligible population and the indications for SCT by reducing the incidence of early transplantation-related complications. One can intuitively expect that RIC will also reduce the incidence of second malignancies [6]. However, older patients, who have often had more prior chemotherapy, including a prior autologous SCT, are included in RIC studies. High-dose TBI is not used; however, low-dose TBI or chemotherapy may be even more carcinogenic as they may leave damaged cells viable. Fludarabine, which is a major component of RIC, has been associated with second...
malignancies in patients with lymphatic malignancies, especially when given with alkylating agents [9]. Most importantly, chronic GVHD with the associated prolonged immune suppression, a major risk factor for second malignancies, may not be reduced by RIC. A large comparison of RIC and MAC for AML, reported by the Center for International Blood and Marrow Transplant Research, has shown that the late nonrelapse mortality negates any early decrease in toxicity by RIC, resulting in similar survival. In particular, chronic GVHD and late infections were not reduced with RIC [10]. One could, therefore, also expect similar trends in the incidence of second malignancies. However, due to the relatively limited long-term follow-up so far of RIC recipients, the incidence and risk factors for second malignancies after RIC have not been defined.

In a single-center analysis, we reported the incidence of second malignancies in 931 patients given MAC (n = 257), RIC (n = 449), or fludarabine-based reduced-toxicity myeloablative conditioning (RTC, n = 225) [5]. Twenty-seven patients had a second malignancy, diagnosed a median of 43 months after SCT. The 10-year cumulative incidence was 5.6%, twice the expected rate in a matched normal population. The incidence was 1.7%, 7.4%, and 5.7% after MAC, RIC, and RTC, respectively (P = .02). Multivariate analysis identified fludarabine-based conditioning (hazard ratio [HR], 3.5; P = .05), moderate-severe chronic GVHD (HR, 2.8; P = .01), and diagnosis of chronic myeloproliferative or nonmalignant disease (HR, .2; P = .04) as risk factors for second malignancy. These results suggested that the risk of second malignancies is not reduced and is even possibly increased in the era of fludarabine-based RIC/RTC.

In this issue of *Biology of Blood and Marrow Transplantation*, Ringdén et al. explored the risk of second malignancies in the largest cohort of RIC recipients reported so far, consisting of 4269 patients with leukemia/myelodysplastic syndrome or lymphoma [11]. The 10-year cumulative incidence of all cancers was 3.35%. This risk was not higher than expected in a general matched population. However, there was an increased risk for cancers of the oral cavity/oropharynx, bone, soft tissues, and melanoma. Advanced age was the only independent predicting factor (HR, 3.1 for age > 50 years). Among patients ages 40 to 60 years old, there was no difference in the incidence of second malignancies between RIC and MAC in leukemia/myelodysplastic syndrome patients and there was a trend for lower incidence after RIC in lymphoma patients.

These observations suggest that second malignancies remain a risk after RIC, at least in certain sites. The risk increases with follow-up, similar to the MAC setting with no apparent plateau and probably with the same kinetics. The involved sites are also similar after RIC and MAC. RIC reduces the acute toxicity of SCT but not the incidence and severity of chronic GVHD and other late effects that are related to transplantation immunobiology. The comparison of the incidence of second malignancies after RIC and MAC remains inconclusive, as second cancers may become apparent more than 10 years after SCT and a longer follow-up of a larger cohort may be required. Patients and physicians should be aware of this association and life-long cancer screening is required for all transplantation survivors.

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