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Second neoplasms in adult patients submitted to haematopoietic stem cell transplantation☆

Anna Torrent*, Christelle Ferrá, Mireia Morgades, María-José Jiménez, Juan-Manuel Sancho, Susana Vives, Montserrat Batlle, Miriam Moreno, Blanca Xicoy, Albert Oriol, Gladys Ibarra, Josep-Maria Ribera

Servicio de Hematología Clínica, Institut Català d'Oncologia-Hospital Germans Trias i Pujol, Institut de Recerca contra la Leucèmia Josep Carreras, Universitat Autònoma de Barcelona, Badalona, Barcelona, Spain

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ABSTRACT

Background and objective: Patients submitted to haematopoietic stem cell transplantation (HSCT) are at increased risk of late complications, such as second neoplasm (SN). The incidence and risk factors of SN in patients receiving HSCT at a single centre were analyzed.
Patients and methods: The follow-up of adult patients who received a first HSCT (autologous [auto-HSCT] or allogeneic [allo-HSCT]) between January 2000 and December 2015 was reviewed. We collected their demographic characteristics, the primary disease and type of HSCT, and analyzed the cumulative incidence of SN and their risk factors.
Results: Of 699 transplanted patients (auto-HSCT, n = 451; allo-HSCT, n = 248), 42 (6%) developed SN (17 haematological and 25 solid), 31 post-auto-HSCT and 11 post-allo-HSCT. Haematologic SN were more frequent after auto-HSCT than after allo-HSCT. The median time between HSCT and SN was 4.09 years [range 0.07–13.15], with no differences between auto-HSCT and allo-HSCT. The cumulative incidence of SN was 5% (95% CI 3–6) at 5 years, 7% (95% CI 5–10) at 10 years and 11% (95% CI 8–15) at 15 years, without differences according to the type of HSCT. Only the age over 40 years correlated with an increased risk of SN.
Conclusions: In this series, the incidence of post-HSCT SN was similar to that previously described. Patients submitted to an auto-HSCT showed a higher frequency of haematologic SN. A higher incidence of SN was detected in patients older than 40 at the time of HSCT.

Segundas neoplasias en pacientes adultos receptores de un trasplante de progenitores hematopoyéticos

Palabras clave:
Trasplante de progenitores hematopoyéticos
Segundas neoplasias
Tumores sólidos
Neoplasias hematológicas

RESUMEN

Fundamento y objetivo: Los receptores de un trasplante de progenitores hematopoyéticos (TPH) tienen un mayor riesgo de complicaciones tardías, como las segundas neoplasias (SN). Se analizó la incidencia de SN en pacientes receptores de un TPH en un centro.
Pacientes y métodos: Estudio retrospectivo de pacientes adultos receptores de un primer TPH (autogénico [auto-TPH] o alogénico [alo-TPH]) entre enero de 2000 y diciembre de 2015. Se recogieron sus características demográficas, la enfermedad de base y el tipo de TPH, y se analizó la incidencia acumulada de SN y sus factores de riesgo.
Resultados: De 699 pacientes receptores de un auto-TPH (n = 451) o alo-TPH (n = 248), 42 (6%) desarrollaron una SN (17 hematológicas y 25 sólidas), 31 postauto-TPH y 11 postalo-TPH. Se observó un mayor número de SN hematológicas tras auto-TPH que tras alo-TPH. La mediana de tiempo entre el TPH y la SN fue de 4,09 años [extremos 0,07-13,15], sin diferencias

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* Corresponding author.
E-mail address: atorrent@iconcologia.net (A. Torrent).

entre auto-TPH y alo-TPH. La incidencia acumulada de SN post-TPH fue de 5% (IC 95% 3-6) a 5 años, 7% (IC 95% 5-10) a 10 años y 11% (IC 95% 8-15) a 15 años, sin diferencias en función del tipo de TPH. Solo la edad superior a los 40 años se correlacionó con un mayor riesgo de SN.
Conclusiones: En esta serie, la incidencia de SN post-TPH fue similar a la descrita. Los receptores de un auto-TPH presentaron mayor frecuencia de SN hematológicas. Se detectó una mayor incidencia de SN en pacientes de más de 40 años en el momento del TPH.

Introduction

The improvement in the indications and in the procedure of hematopoietic stem cell transplantation (HSCT) has increased the number of long-term survivors. However, these patients are at risk of developing late complications, including second neoplasms (SN). The studies carried out to date have documented that survivors of HSCT, both autologous (auto-HSCT) and allogeneic (allo-HSCT), have a higher risk of developing a SN, with a cumulative incidence ranging between 5 and 21% after 10 years. This incidence continues to increase in the longer-term studies, without observing a plateau in the incidence curves.[1–8] Several factors have been described that contribute to the increase in the incidence of SN, including advanced age at the time of HSCT, total body irradiation (TBI) as part of the conditioning regimen, the cytostatic treatments used before and during HSCT, and graft-*versus*-host disease (GvHD) and its maintained immunosuppressive treatment, among others.[1–4,9]

Post-HSCT SNs can be divided into 3 subtypes: post-transplant lymphoproliferative syndromes (PTLS), acute leukemias and myelodysplastic syndromes (AL/MDS) and solid neoplasms. The time of onset of SN is variable, with a relatively early development of haematological neoplasms, which are usually observed from a few months (especially PTLS) to 4–5 years, while solid tumours have a longer latency, 6–8 years, according to studies.[1,2,10–12]

The most frequent malignancies observed in patients receiving a HSCT are those located at oropharyngeal level, especially if they have severe chronic GvHD or receive prolonged immunosuppressive treatment.[13] It has also been documented an increased risk of SN in the liver, central and peripheral nervous system, thyroid, bone, soft tissue and skin (melanomas). In the largest study of solid SN after auto-HSCT published to date, numerous sarcomas were also observed in locations other than bone and soft tissues, such as liver, small intestine, lung, uterus and cervix.[1] Several studies have found a relationship between squamous neoplasms and the presence of moderate or severe chronic GvHD.[1,2,7,14,15] On the other hand, TBI has been related to the appearance of non-squamous solid neoplasms, especially in young patients and over-5-year survivors since the HSCT.[1]

The objective of this study was to analyze the incidence and type of SN after HSCT in a single centre, and to identify associated risk factors.

Patients and methods

Retrospective study of 699 adult patients (≥18 years) recipients of a first HSCT (autologous or allogeneic) between January 2000 and December 2015 in a single centre. The following variables were recorded and analyzed: age, sex, underlying disease, history of previous neoplasm, state of the disease which indicated the HSCT, treatment prior to HSCT, type of HSCT, source of hematopoietic stem cells, conditioning treatment, immunosuppressive therapy, GvHD acute or chronic and its degree, as well as the type and location of the SN. The overall survival (OS) of the patients was calculated from the time of HSCT and from the moment of SN. In the patients who received more than one HSCT, the variables analyzed, and survival were considered from the time of the first HSCT. Also, possible factors influencing the cumulative incidence of SN, both solid and haematological, were studied.

All SN that appeared after the day of the hematopoietic progenitor cell infusion were considered, except skin carcinomas *in situ* and the basal cell type.

A descriptive study of the main demographic and clinical variables was carried out. The Kruskal–Wallis tests or the median test (continuous variables) and the chi-square Pearson or Fisher's exact tests (categorical variables) were used to perform the comparison between groups. OS was defined as the time elapsed between HSCT and death or the patient's last control, and OS after SN was defined as the time interval between SN diagnosis and death or last control. Both were calculated using the Kaplan–Meier method and the comparisons were made using the log-rank test. The cumulative incidence of SN was calculated as the time elapsed between the HSCT and the SN, considering as a competitive episode any death which was not related to SN. The estimate was calculated using cumulative incidences and the Gray's test was used for comparisons. All statistical analyses were performed using the SPSS® *software*, version 23 and the R® *software* version 3.3.2. The level of statistical significance was established in $p < 0.05$.

Results

Of the 699 consecutive patients 18 years of age or older who received a first HSCT between January 2000 and December 2015, 451 had an auto-HSCT and 248 an allo-HSCT. Table 1 describes the demographic and clinical characteristics, the type of underlying disease and its treatment, the characteristics of HSCT and the progression both in the global series and in patients who developed or not SN. Both groups are comparable, although there was a tendency to present more SN in patients with lymphoma as a disease supporting HSCT.

Forty-two of the 699 patients (6%) developed a SN, 31 after an auto-HSCT and 11 after an allo-HSCT (Table 2). Two of the 42 patients developed a third neoplasm, and in another 2 the SN developed after the second HSCT. The characteristics of SNs according to the type of HSCT are described in Table 2. Both groups of SN are comparable, except for a tendency to observe a more advanced age in patients receiving an auto-HSCT compared to recipients of an allo-HSCT, a fact possibly related to the upper age limit for the indication of both types of HSCT. In addition, a greater number of haematological SN was observed after auto-HSCT than after allo-HSCT.

The haematological SNs (n = 17) were 13 therapy-related acute myeloid leukemias (AML) or MDS (t-AML/MDS) and 4 PTLS. Of the 9 AMLs diagnosed, 6 had a complex karyotype, 2 had cytogenetics of poor prognosis and one did not show any cytogenetic or molecular alteration. Five patients with AML did not receive treatment because of a poor general condition or associated comorbidities, and 4 were treated with curative intent, 2 of which are still alive after a second HSCT. Of the 4 patients with MDS, 3 had a high risk IPSS, and the remainder was low risk, not requiring treatment. Two of the 3 patients with high-risk IPSS did not receive treatment due to