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Kinetics of the use of cryopreserved autologous stem cell grafts: a GITMO-SIDEM survey

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Abstract

Background aims. Hematopoietic stem cell cryopreservation significantly contributed to autologous stem cell transplantation (ASCT). Cryopreserved stem cell units (SCU) are expected to be used soon after harvesting for most purposes, but, in a number of cases, they remain stored for some time, creating an increasing load for SCU depositories. Disposal policies vary widely in each center, and the existing guidelines are insufficient. *Methods.* We conducted a survey of seven Gruppo Italiano Trapianto di Midollo Osseo centers to investigate the outcome of SCU harvested from January 2005 to December 2009 for ASCT. The data from 1603 collections were gathered, for a total of 5822 SCU. *Results.* In our cohort, 79% of patients collected $>5 \times 10^6$ CD34+ cells/kg, and 3.4% collected $<2 \times 10^6$ CD34+ cells/kg. Up to 21% of all the patients and 42% of those with acute leukemia did not undergo reinfusion, and 37% of the cryopreserved SCU were excess, resulting from patients not reinfusing or partially reinfusing. Less than one-third of the excess SCU was disposed, and the major causes of disposal were death and, in a minority of cases, withdrawal of the indication for ASCT. In our analysis, very few first reinfusions occurred after 2 years, and those after 5 years were exceptional. Through the use of a multivariate analysis, we sought to identify the risk factors for collection non-use, independent of the centers' policies. Non-use of SCU was significantly associated with patients with acute leukemia, collections of $<2 \times 10^6$ CD34/kg and lower age groups. *Conclusions.* These data serve as a valid basis to support rational recommendations for cost-effective storage and disposal of SCU.

Key Words: *biological specimen banks, cryopreservation, hematopoietic progenitor cells, hematopoietic stem cell transplantation, long-term storage, medical waste disposal*

Introduction

Autologous hematopoietic stem cell transplantation (ASCT) is an important treatment modality for numerous malignant hematologic and non-hematologic disorders. There has been a steady increase in the number of autologous procedures performed worldwide in the past 10 years (1). The major advantages of ASCT over allogeneic transplantation are lower toxicity, lower overall procedure costs and immediate availability of the graft (2). Cryopreservation significantly contributed to the application and flexibility of ASCT, allowing for optimization of the times and modalities of collection and reinfusion. Cryopreserved units are expected to be used soon after harvesting for most purposes, but, in recent years, indications for preventive stem cell harvesting have been expanded. Particularly in the setting of multiple myeloma (MM), double ASCT has become

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a standard approach for young patients seeking a long-term remission (3,4), thus requiring collection of a sufficient amount of hematopoietic progenitor cells (HPC) to guarantee hematopoietic recovery after two aplastic phases. In patients relapsed after ASCT, the reapplication of high-dose melphalan followed by a third ASCT is a valuable option, especially among patients who achieved a durable response after the first treatment (5,6).

In other cases, autologous cells remain stored longer than expected because the indication for ASCT declined in the time between the collection and conditioning. This situation occurs because of a patient's death or because of complications or other clinical factors (ie, unsatisfactory response to induction therapy) that disproportionately increase the risk-benefit ratio of the ASCT procedure or because of a changed indication (ie, decision to perform allogeneic transplant). In the case of a patient's death, it is clear that the stored HPC are not useful for therapeutic purposes, but in the latter two cases, disposal of the non-used units may cause loss of a therapeutic opportunity and may be considered unethical (7). The prolonged storage of non-used units is an increasing burden for stem cell depositories and raises serious economic concerns. The identification of the time at which HPC can or should be eliminated involves a number of technical, clinical, ethical and economic considerations, each of which should be adequately weighed to guide the preparation of consensus recommendations. The policies for the disposal of autologous cells affect the size and the cost of the stem cell biobank and concurrently may determine whether the patients who may need a late reinfusion will benefit from their stored cells.

The data on the long-term engraftment ability of cryopreserved stem cell units (SCU) are contradictory, and it is impossible to define exactly the maximum period of cryopreservation before stored SCU become unacceptable for reinfusion. Two studies (8,9) that investigated surrogate biological markers of potential engraftment after a median of 9.5 and 15 years found that deterioration of stem cell quality and viability may occur and that many of the long-term stored SCU may not be adequate for transplantation. A recent Canadian study did not find any difference in terms of count recoveries and other graft outcomes between short-term and long-term (median, 45 months; up to 7 years) storage of cryopreserved hematopoietic stem cells (10).

The deficit of official recommendations or consensus about these issues and the absence of data about the current status of stem cell depositories prompted a joint GITMO (Italian Group for Bone Marrow, Hematopoietic Stem Cell Transplantation and Cell Therapy)−SIDEM (Italian Society of Hemapheresis and Cell Therapy) expert panel to conduct a survey of seven GITMO centers, with the aim of investigating in a representative clinical setting the outcome of all the cryopreserved units obtained for ASCT from apheresis of the patients mobilized with growth factor and/or chemotherapy. Seven GITMO centers participated in the survey. The time frame was from January 2005 to December 2009 to ensure a significant minimal follow-up and to warrant a lower incidence of missing data because all the centers had electronic registries in these years.

Methods

A GITMO-SIDEM meeting to establish a common policy about the disposal of cryopreserved autologous stem cells was held in Bologna in June 2012. The participants agreed that a relevant drawback to writing a consensus recommendation was the deficit of sufficient data depicting the current status of stem cell depositories. The committee decided to conduct a survey in a representative sample of the Italian GITMO-SIDEM centers, and seven centers were asked to fill a database centered on single collections (ie, one collection could include one or more leukapheresis procedures on subsequent days) performed from January 2005 to December 2009. A total of 1603 collections were collected from 1529 patients, with 74 repeated collections from the same patients. The collections were considered split if the first and last leukapheresis occurred more than 30 days apart. Because repeated collections may refer to different settings/indications for the same patient, we will refer to these 1603 cases as patients. The dataset was updated to July 2012. Information in the dataset included the patient's characteristics including the following: identification, date of birth, diagnostic category; the collection procedure (number of leukapheresis procedures performed, number of units frozen, total amount of CD34+ cells frozen); and subsequent use/non-use of the cryopreserved units (including instances of damaged units).

Statistical analysis

The responses from each center were merged into a single database and analyzed. Descriptive statistics were performed for all the variables in the datasets and are reported in Table I. The rates and proportions were compared with the use of χ^2 or Fisher's exact test. The time-dependent variables generated from the raw data were the time to first reinfusion (in days, from the date of the first