Optimal timing of allogeneic hematopoietic stem cell transplantation in patients with myelodysplastic syndrome

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Allogeneic hematopoietic stem cell transplantation (HSCT) represents the only curative treatment for patients with myelodysplastic syndrome (MDS), but involves non-negligible morbidity and mortality. Registry studies have shown that advanced disease stage at transplantation is associated with inferior overall survival. To define the optimal timing of allogeneic HSCT, we carried out a decision analysis by studying 660 patients who received best supportive care and 449 subjects who underwent transplantation. Risk assessment was based on both the International Prognostic Scoring System (IPSS) and the World Health Organization classification-based Prognostic Scoring System (WPSS). We used a continuous-time multistate Markov model to describe the natural history of disease and evaluate the effect of allogeneic HSCT on survival. This model estimated life expectancy from diagnosis according to treatment policy at different risk stages. Relative to supportive care, estimated life expectancy increased when transplantation was delayed from the initial stages until progression to intermediate-1 IPSS-risk or to intermediate WPSS-risk stage, and then decreased for higher risks. Modeling decision analysis on WPSS versus IPSS allowed better estimation of the optimal timing of transplantation. These observations indicate that allogeneic HSCT offers optimal survival benefits when the procedure is performed before MDS patients progress to advanced disease stages. Am. J. Hematol. 88:581–588, 2013. © 2013 The Authors American Journal of Hematology Published by Wiley Periodicals, Inc.

Introduction
Myelodysplastic syndromes (MDS) are myeloid neoplasms that present as refractory cytopenia and typically occur in elderly people [1]. Because of population aging, MDS represent one of the most common hematologic malignancies in Western countries nowadays, their annual incidence exceeding 20 per 100,000 persons over the age of 60 years [1].

MDS are highly heterogeneous from a clinical point of view, ranging from conditions with a near-normal life expectancy to forms approaching acute myeloid leukemia (AML) [2]. This clinical heterogeneity reflects different somatic mutations responsible for clonal proliferation of myelodysplastic stem cells [3–5]. In particular, spliceosome mutations, implying abnormalities of mRNA splicing in the pathogenesis of MDS, have variable prognostic relevance, depending on the mutated splicing factor [6–9].

From a practical point of view, the definition of individual risk requires the use of prognostic models. In 1997, Greenberg et al. developed the International Prognostic Scoring System (IPSS) [10], which has rapidly become a benchmark for clinical decision-making, clinical trials, and drug approval. Despite its usefulness, this scoring system has weaknesses [11], and has been recently revised with the development of the IPSS-R [12]. Following the introduction of the World Health Organization (WHO) classification of MDS [13], a WHO classification-based Prognostic Scoring System (WPSS) was defined, based on WHO categories, cytogenetic abnormalities, and transfusion-dependency [14,15]. WPSS proved to be able to provide dynamic prognostic information at any time of the disease course, and to predict the outcome of allogeneic hematopoietic stem cell transplantation (HSCT) [16].

Despite recent therapeutic progress, the only curative treatment for MDS patients remains allogeneic HSCT, which is considered as a conventional therapeutic option until the age of 65 in eligible patients. Its efficacy, however, is considerably limited by morbidity and mortality, resulting in a long-term survival rate of about 30% [17]. Several issues must be taken into account.
when considering allogeneic HSCT and evaluating its benefits in the individual patient with MDS, and a crucial question is timing of transplantation [18]. Considering the clinical course of MDS, the optimal timing of allogeneic HSCT would be a disease stage that provides the best overall life expectancy, accounting for both pretransplantation and posttransplantation survival. In fact, patients at early stages, especially those with a somatic mutation of SF3B1, may experience long periods with stable disease after diagnosis [2,6], and the risks of morbidity and mortality related to allogeneic HSCT would be unacceptably high for many of them.

However, a number of studies have shown that advanced disease stage at transplantation is associated with inferior overall survival [16,17]. In particular, a recent study of the European Group for Blood and Marrow Transplantation clearly showed that advanced disease stage at transplantation was the major independent variable associated with an inferior 4-year overall survival in MDS patients 50 years or older [17]. However, a previous decision analysis by the International Bone Marrow Transplant Registry (IBMTR) concluded that, whereas immediate transplantation was associated with maximal life expectancy and survival in patients with intermediate-2- and high IPSS risk, for those with low and intermediate-1 IPSS-risk delayed transplantation offered optimal survival benefit [19]. It was therefore concluded that the optimal timing of transplantation was at the time of disease progression from lower to higher IPSS risk groups. This study has substantially influenced clinical practice despite a number of intrinsic limitations [11]. In particular, the IBMTR analysis considered patients at the time of MDS diagnosis, ignoring changes in their disease status that frequently occur before transplantation or leukemic evolution.

To overcome the above limitations, we carried out an ad hoc decision analysis in MDS patients aged up to 65 years, classified according to WHO criteria and stratified according to either the IPSS or WPSS risk. We used a continuous-time multistate Markov model to describe the natural history of disease and evaluate the effect of allogeneic HSCT on survival at different stages of disease.

Methods

Patients and study design

These investigations were approved by the Ethics Committee of the Fondazione Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Policlinico San Matteo, Pavia, Italy. All procedures were carried out in accordance with the ethical standards of the Declaration of Helsinki.

We analyzed two cohorts comprising 1137 MDS patients. The first cohort (Pavia cohort) included 660 patients diagnosed with MDS according to WHO criteria [13,20] at the Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, between 1992 and 2009. The second cohort (GITMO cohort) included 477 undergoing allogeneic HSCT for primary MDS or AML evolved from MDS between 1997 and 2009, and reported to the GITMO registry (Table I). Secondary AML was included in this analysis since this condition is very close to RAEB-2, and not infrequently defined as refractory anemia with excess of blasts in transformation (RAEB-T), characterized by 20–29% blasts in the bone marrow [21]. Different conditioning regimens and different donor types had been employed as shown in Supporting Information Table I.

Disease-related risk was evaluated by using both the IPSS [10] and WPSS [14]. With respect to this latter, we used the original prognostic model that included transfusion dependency, as this parameter has proved to have relevant prognostic significance for the outcome of allogeneic HSCT [22].

In the Pavia cohort, patients were essentially treated with best supportive care and regularly followed-up, and this allowed clinical data and disease staging to be monitored longitudinally. In the GITMO cohort, all clinical variables were analyzed at the time of transplantation in patients undergoing allogeneic HSCT upfront, and at the time of remission-induction chemotherapy in those receiving treatment before allogeneic HSCT (Table I, and Supporting Information Table I).

Decision strategy

We adopted a continuous-time, multistate Markov approach to model the course of the disease in MDS patients and to assess the effect of allogeneic HSCT on overall survival [23,24]. A multistate model describes how an individual moves between a series of states in time. Markov models are multistate models based on Markov processes, that is, stochastic processes with the property that the probability of moving to a particular state in the future only depends on this state and not on past states. Further information on Markov models is reported in Supporting Information Methods. A continuous-time Markov model was used to estimate the risk of progression from each disease state to the next one. We fitted two models based on IPSS and WPSS risk, respectively (Fig. 1). Each risk category was represented by a state in the model, and death was considered as absorbing state. That is, a state in which transitions to other states are not allowed. Transitions were allowed from any IPSS category to the next one, to AML and to death. Transition intensity, that is, the instantaneous risk of moving to a particular state in the future only depends on this state and not on past states. Further information on Markov models is reported in Supporting Information Methods.

| TABLE I. Clinical Characteristics of MDS Patients Belonging to the Pavia Cohort, Who Received Best Supportive Care, and to the GITMO Cohort, Who Had Received Allogeneic HSCT |
|---------------------------------|-----------------|-----------------|
| **Clinical characteristics**    | **Pavia cohort**| **GITMO cohort**|
| Number of patients              | 660             | 337             |
| Age (completed years; median)   | 63 (11–92)      | 48 (13–69)      |
| WHO classificationb              |                 |                 |
| RARS                           | 76 (12%)        | 11 (3%)         |
| MDS del (5q)                   | 42 (6%)         | 4 (1%)          |
| Intermediate-1                  | 277 (41%)       | 118 (35%)       |
| Intermediate-2                  | 372 (57%)       | 139 (41%)       |
| High                           | 53 (8%)         | 37 (11%)        |
| WPSS risk                       |                 |                 |
| Very-low                       | 142 (21%)       | –               |
| Low                            | 183 (28%)       | 34 (10%)        |
| Intermediate                   | 117 (18%)       | 74 (22%)        |
| High                           | 176 (27%)       | 185 (55%)       |
| Very high                      | 42 (6%)         | 44 (13%)        |

In the Pavia cohort, all clinical variables were analyzed at the time of diagnosis. In the GITMO cohort, clinical variables were analyzed at the time of transplantation in patients undergoing upfront allogeneic HSCT, and at the time of remission-induction chemotherapy in those receiving treatment before transplantation.

b Including patients affected with RAEB in transformation according to the FAB classification.

b RCDU, refractory cytopenia with unilineage dysplasia; RARS, refractory anemia with ring sideroblasts; MDS del(5q), myelodysplastic syndrome with del(5q); RCMO, refractory cytopenia with multilineage dysplasia; RAEB-1, refractory anemia with excess blasts type 1; RAEB-2, refractory anemia with excess blasts type 2.
younger (P < 0.001), as shown in Fig. 2C.D.

In an exploratory multivariate survival analysis, type of donor (HLA-identical sibling versus matched unrelated donor) and conditioning regimen (standard versus reduced-intensity) did not significantly affect posttransplantation survival (P = 0.064 and P = 0.757, respectively; P = 0.759 for interaction). Therefore, all types of donor and conditioning regimen were included in the subsequent decision analysis.

Decision analysis
We fitted two models of the clinical course of MDS, where patients were stratified according to the IPSS and WPSS, respectively. We first analyzed the goodness of fit of the IPSS- and the WPSS-based Markov models by comparing the estimated survival curves to the Kaplan-Meier estimates. No major lack of fit was detected in either model, as illustrated in Supporting Information Fig. 3.

We then focused on the effect of allogeneic HSCT on survival. In the lower IPSS and WPSS risk groups, the HRs after transplantation were very high due to the risk of NRM, as compared with a relatively low mortality in non-transplanted patients. This was not observed in higher IPSS and WPSS risk categories, in which mortality in non-transplanted subjects was much higher. The HRs associated with transplantation is reported in Supporting Information Table II. The expected survival after diagnosis according to the IPSS and WPSS models was calculated for different transplant policies to assess the optimal transplantation timing.

IPSS-based transplantation policies
Using the IPSS model, we analyzed the following three policies: (i) policy 1: to perform transplantation in state 1 (low IPSS risk) at t months since diagnosis (range 0–60 months) or immediately in case of disease progression before the planned delay time t; (ii) policy 2: not to perform transplantation in state 1 and do it in state 2 (intermediate-1 IPSS risk) at t months since entering this state (range 0–60 months) or immediately in case of disease progression before the planned delay time t; (iii) policy 3: not to perform transplantation in state 1 or 2, and do it in state 3 (intermediate-2 IPSS risk) at t months since entering this state (range 0–60 months) or immediately in case of disease progression before the planned delay time t. Each policy was evaluated for a set of different ages at diagnosis (between 30 and 65 years with 5-year intervals), and patients lost eligibility to transplantation at 65 years of age.

Gains or losses in life expectancy estimated with respect to a nontransplantation policy are reported in Fig. 3 and Table II, while the obtained life expectancy point estimates under different policies are listed in Supporting Information Table III. Life expectancy increased with increasing delay time of transplantation according to policy 1, but it was overall lower than that estimated according to policy 2 (to delay transplant until progression to intermediate-1 IPSS risk). After progression to this latter risk, life expectancy progressively decreased while delaying transplantation. Delaying transplantation after progression to intermediate-2 IPSS (policy 3) resulted in lower values for life expectancy compared to those estimated according to policy 2, irrespective of the delay time t.

WPSS-based transplantation policies
Using the WPSS model, we analyzed three policies: (i) policy 1: not to perform transplantation in state 1 (very low

Results
Outcome of MDS patients classified according to IPSS and WPSS
In the Pavia cohort, IPSS and WPSS, both analyzed as time-dependent covariates, significantly stratified the probability of survival of MDS patients (P < 0.001), as shown in Fig. 2A,B. The cumulative incidences of disease progression, transplantation, and death, analyzed as competing risks for each IPSS and WPSS category, are reported in Supporting Information Fig. 2.

Compared with the Pavia cohort, the GITMO cohort was younger (P < 0.001) and included many more subjects with higher IPSS or WPSS risk (P < 0.001). IPSS and WPSS at the time of transplantation significantly stratified posttransplantation survival (P < 0.001), as shown in Fig. 2C.D.

Figure 1. Markov continuous-time multistate models of the natural history of MDS. IPSS (A) and WPSS (B) risk scores were adopted as time-dependent indicators of the natural course of MDS. Allogeneic HSCT was modeled as a time-dependent covariate, and its effect on survival was estimated as a HR with respect to the “no allogeneic HSCT” category. Solid arrows represent transitions according to the natural course of the disease, while the effect of allogeneic HSCT on transition is represented in each state by a dashed arrow.

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Figure 2. Overall survival of MDS patients. Upper part: overall survival of patients belonging to the Pavia cohort stratified according to time-dependent IPSS (A) or time-dependent WPSS (B). Lower part: overall survival of patients belonging to the GITMO cohort stratified according to IPSS (C) or WPSS (D) scores evaluated at the time of allogeneic HSCT. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Figure 3. Gain in expected survival since diagnosis according to IPSS and WPSS models under different transplant policies with respect to a nontransplantation policy. We assumed that the MDS patient was classified as low IPSS or very low WPSS risk at the time of diagnosis. Each policy was then evaluated for a set of different ages at diagnosis (between 30 and 65 years, with 5-year intervals, as shown in the boxes) and for different waiting times \( t \) (between 0 and 60 months since entering any disease state). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]
WPSS risk) and do it in state 2 (low WPSS risk) at 0 months since entering this state (range 0–60 months) or immediately in case of disease progression before the planned delay time \( t \); (ii) policy 2: not to perform transplantation in state 1 or 2, and do it in state 3 (intermediate WPSS risk) at 0 months since entering the state (range 0–60 months) or immediately in case of disease progression before the planned delay time \( t \); (iii) policy 3: not to perform transplantation in state 1 to 3, and do it in state 4 (high WPSS risk) at 0 months since entering the state (range 0–60 months) or immediately in case of disease progression before the planned delay time \( t \). Each policy was evaluated for a set of different ages at diagnosis (between 30 and 65 years with 5-year intervals), and patients lost eligibility to transplantation at 65 years of age.

Under policy 1 (transplantation in low WPSS risk), life expectancy increased with increasing delay in transplantation, at least for patients under the age of 60 (Supporting Information Table III): the younger the patient, the higher the gain in life expectancy (Fig. 3). Under policy 2 (transplantation in intermediate WPSS risk), the gain in life expectancy obtained with immediate transplantation in intermediate state (\( t = 0 \)) was comparable to that obtained with a 60-month delay under policy 1. Delaying transplantation in intermediate WPSS risk resulted in loss of life expectancy at any age (Table II and Fig. 3). Delaying transplantation after progression to high WPSS risk (policy 3) resulted in a lower life expectancy compared to that estimated under policy 2 (Table II and Fig. 3).

### QoL adjusted life expectancy

Adjustment for QoL did not affect the outcome of transplantation for any of the IPSS and WPSS risk groups (see QALY-adjusted life expectancies in Supporting Information Table III).

#### IPSS-versus WPSS-based transplantation strategies

To evaluate the extent to which making a decision based on WPSS versus IPSS may lead to a different transplantation strategy in lower MDS risks, we cross-tabulated the distribution of patients in the Pavia cohort according to their IPSS and WPSS scores. Among patients who at any point during follow-up were classified as low IPSS risk and were therefore candidates to a delayed transplantation according to an IPSS-based strategy, 13% had an intermediate or high WPSS score (Fig. 4), and would consequently benefit from an immediate transplantation according to a WPSS-based strategy. This subgroup specifically included patients with multilineage dysplasia and/or transfusion-dependency.

Among patients who were classified as intermediate-1 IPSS risk and were therefore candidates to immediate transplantation according to an IPSS-based strategy, 34% had a very low or low WPSS risk (Fig. 4), and would consequently be candidates to delayed transplantation according to a WPSS-based strategy. This subgroup included patients without excess of blasts or without poor risk cytogenetics.

We then compared the life expectancy estimated under the best IPSS-based strategy (i.e., transplantation immediately after entering the intermediate-1 risk group) with that estimated under the best WPSS-based strategy (i.e., transplantation immediately after entering the intermediate risk group). Overall, there was a 4-year gain in life expectancy.

**TABLE II. Estimated Gains or Losses in Life Expectancy (Years) According to Different Transplantation Policies and Variable Patient’s Age**

| IPSS-based transplantation policies | Patient’s age (years) | WPSS-based transplantation policies | Patient’s age (years) |
|-----------------------------------|-----------------------|-----------------------------------|-----------------------|
|                                   | Delay time (months)   | 40      | 50      | 60      | Delay time (months)   | 40      | 50      | 60      |
| Policy 1: transplantation in low IPSS risk | 0                    | -0.60  | -0.60  | -0.60  | Policy 1: transplantation in low WPSS risk | 0        | 7.05   | 6.53   | 3.97   |
|                                   | 12                   | 0.09   | 0.09   | 0.09   | 12                   | 7.82   | 7.16   | 3.88   |
|                                   | 24                   | 0.71   | 0.71   | 0.71   | 24                   | 8.44   | 7.64   | 3.68   |
|                                   | 48                   | 1.80   | 1.80   | 1.80   | 48                   | 9.34   | 8.27   | 3.05   |
|                                   | 60                   | 2.27   | 2.27   | 2.27   | 60                   | 9.67   | 8.48   | 2.67   |
| Policy 2: transplantation in intermediate-1 IPSS risk | 0                    | 6.37   | 5.38   | 2.67   | Policy 2: transplantation in intermediate WPSS risk | 0        | 10.77  | 8.66   | 2.67   |
|                                   | 12                   | 5.11   | 4.25   | 1.82   | 12                   | 7.29   | 5.67   | 1.33   |
|                                   | 24                   | 4.18   | 3.41   | 1.21   | 24                   | 5.15   | 3.88   | 0.68   |
|                                   | 48                   | 2.95   | 2.32   | 0.51   | 48                   | 3.04   | 2.18   | 0.28   |
|                                   | 60                   | 2.58   | 2.00   | 0.32   | 60                   | 2.55   | 1.81   | 0.25   |
| Policy 3: transplantation in intermediate-2 IPSS risk | 0                    | 1.44   | 1.09   | 0.32   | Policy 3: transplantation in high WPSS risk | 0        | 2.24   | 2.18   | 0.73   |
|                                   | 12                   | 1.08   | 0.79   | 0.19   | 12                   | 1.63   | 1.30   | 0.20   |
|                                   | 24                   | 0.96   | 0.69   | 0.16   | 24                   | 1.39   | 1.00   | 0.09   |
|                                   | 48                   | 0.91   | 0.65   | 0.16   | 48                   | 1.28   | 0.87   | 0.10   |
|                                   | 60                   | 0.90   | 0.65   | 0.15   | 60                   | 1.26   | 0.86   | 0.09   |
Using the WPSS-based policy, and this gain was maximized in younger patients (Table II).

Discussion
Patients with MDS may be diagnosed at any stage of the disease, and their life expectancy may vary from several years to few months according to the disease-related risk, which can be assessed using the IPSS or WPSS as shown in Fig. 2 [10,14]. The risk stage is also very relevant to the outcome of allogeneic HSCT, since patients with lower IPSS or WPSS risks have much better posttransplantation survival than those with higher risks, as shown in Fig. 2C,D. These findings confirm previous observations that transplantation early after diagnosis of MDS is associated with the most favorable outcome [16,17,29–31].

The decision analysis by the IBMTR based on a discrete-time Markov model concluded that life expectancy of patients with low or intermediate-1 IPSS risk at diagnosis was higher when transplantation was delayed but performed before the progression of AML [19]. This conclusion is difficult to reconcile with the survival data reported in Fig. 2C, showing that MDS patients transplanted at the intermediate-1 IPSS risk have a much better outcome than patients transplanted at the intermediate-2 IPSS risk stage. We believe that the IBMTR analysis had weaknesses mainly related to the unavailability of longitudinal clinical data. In fact, clinical features of the nontransplantation cohort were only available at diagnosis and at the time of leukemic evolution or death. Therefore, the model adopted did not account for disease progression from lower to higher risk stages, which is typical of the natural course of disease and may significantly affect clinical outcome.

This study included a cohort of untreated MDS patients with detailed longitudinal clinical data previously used to develop the WPSS [14]. On this basis, we adopted a continuous-time Markov approach to model the natural course of disease, while data on transplanted patients from the GITMO registry were used to estimate the effect of transplantation on survival [16]. The output form of the Markov model allowed us to estimate life expectancies under different transplantation policies, and to compare them with a nontransplantation policy.

Using IPSS for risk assessment, the estimated life expectancy increased when transplantation was delayed until progression from low to intermediate-1 risk, and then decreased with further risk increments. These findings are at variance with those of the IBMTR study [19], mainly in that our analysis did no show any advantage in delaying transplantation in the intermediate-1 risk group. These observations have relevant clinical implications, as patients with intermediate-1 IPSS accounted for about half of all MDS patients reported to IBMTR in 2002 [31].

We then tested a transplantation policy based on WPSS, which was shown to improve the prognostic stratification of low-grade MDS and significantly stratify the outcome of transplantation [16]. Using WPSS, the estimated life expectancy was maximized when transplantation was delayed until progression from the very low or low risk to the intermediate risk, and then decreased. Compared with the IPSS, the use of WPSS provided a better evaluation of the optimal timing of transplantation. In fact, the estimated life expectancy provided by the best WPSS-based strategy was 4 year greater that that provided by the best IPSS-based strategy. Within the low IPSS risk, WPSS identifies a subgroup of patients with multilineage dysplasia and/or transfusion-dependency who may benefit from early transplantation. Conversely, within the intermediate-1 IPSS risk, WPSS identifies patients without excess blasts or with favorable cytogenetics who may benefit from a delayed transplantation strategy.

In this study, started 3 years ago, we did not consider the recently developed IPSS-R, which is based on a novel cytogenetic stratification [12]. The IPSS-R needs to be validated in the transplantation setting before an ad hoc Markov model can be developed. It should be noted, however, that it has been recently shown that the 5-group cytogenetic risk classification of the IPSS-R has greater discriminating power for post-transplantation relapse and mortality than the IPSS cytogenetic risk classification [32].

The availability of novel disease-modifying therapies might affect the conclusions of our decision analysis. In a randomized clinical trial, azacitidine was shown to improve survival of patients with higher-risk MDS not eligible for allogeneic HSCT [33]. However, more than 70% of patients in this trial were 65 or older, thus showing little overlap with the population included in our analysis. Moreover, a decision analysis has been recently conducted comparing reduced-intensity allogeneic HSCT versus non-transplantation approaches including azacitidine in MDS patients aged 60–70 years [34]. This study showed that early transplantation offers survival benefit for intermediate-2/high IPSS MDS, that is, the condition for which azacitidine has been approved. There is no evidence so far that this drug can significantly improve survival of MDS patients belonging to lower risk groups.

In summary, the findings of our study, based on modeling of the natural course of MDS, indicate that a delayed...
transplantation strategy is advisable for patients with early disease, that is, with low IPSS and very low or low WPSS risk. Allogeneic HSCT should instead be offered to eligible patients belonging to intermediate risk categories, in particular to those with intermediate-1 IPSS or intermediate-2 WPSS risk, since this strategy offers the best survival benefit (Fig. 5). Finally, modeling decision analysis on WPSS versus IPSS allows a better estimation of the optimal timing of transplantation, especially because the WPSS accounts for transfusion dependency, an independent negative prognostic factor for transplantation outcome.

Appendix

The following institutions in Italy contributed to the trial:

- Division of Hematology, Ospedale “S.S. Antonio e Biagio” Alessandria (A. Levis);
- Division of Hematology, Ospedali Riuniti, Bergamo (A. Rambaldi); Institute of Hematology and Clinical Oncology L.A. Seragnoli, Ospedale S. Orsola-Malpighi, University of Bologna, Bologna (G. Bandini);
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- Division of Hematology and Bone Marrow Transplant Center, Ospedale Oncologico A. Businco, Cagliari (E. Angelucci, D. Baronacci); Bone Marrow Transplantation Unit, Ospedale R. Binagli, University of Cagliari, Cagliari (G. La Nasa);
- Division of Hematology and Bone Marrow Transplantation, Ospedale Ferrarotto* Catania (G. Milone);
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