Stem Cell Transplantation

Granulocyte colony-stimulating factor affects serum levels of soluble interleukin-2 receptors after allogeneic stem cell transplantation

Soluble interleukin-2 receptor (sIL-2R) levels were analyzed in 127 stem-cell transplant recipients. Granulocyte-colony stimulating factor (G-CSF) was given to 57 patients after transplantation. We found an association between G-CSF and increased sIL-2R levels. This indicates increased T-cell activation and may be one reason for the previously found increased incidence of acute graft-versus-host disease in G-CSF-treated patients.

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One of the main obstacles to success in allogeneic hematopoietic stem cell transplantation (HSCT) is graft-versus-host disease (GVHD). To shorten the aplastic phase, many centers use granulocyte colony-stimulating factor (G-CSF).[1] However, reports have shown that G-CSF after HSCT increases acute GVHD and decreases survival.[2,3] Soluble IL-2 receptors (sIL-2R) have been shown to be a marker for T-cell activation[4] and may be used for the diagnosis of GVHD.[5] One hundred and twenty-seven HSCT patients transplanted at Huddinge University Hospital were studied. The characteristics of the donors and recipients are shown in Table 1. The high resolution polymerase chain reaction-single strand polymorphism method was employed for HLA typing. Conditioning consisted of 120 mg/kg cyclophosphamide combined with 12 Gy fractionated total body irradiation or 16 mg/kg busulfan. Some patients received reduced intensity conditioning. Post-transplant immunosuppression consisted of cyclosporine and methotrexate (to maintain blood levels between 200-300 ng/mL during the fisrt month) (i.v. at a dose of 15 mg/m^2 on day +1 and 10 mg/m^2 on days 3, 6 and 11).

Eighty-two patients received peripheral blood stem cells (PBSC) and 45 bone marrow.[6] G-CSF (5 µg/kg/day) was given to 57 consecutive patients from day 10 after HSCT until an absolute neutrophil count >0.5×10^9/L for two consecutive days was reached.[1] Acute GVHD was diagnosed on the basis of clinical symptoms and/or biopsies according to standard criteria. At the first sign of acute GVHD, prednisolone was given for at least one week (2 mg/kg/day). The first blood sample for sIL-2R was drawn 3-5 days after the HSCT and then samples were taken at seven-day intervals until day +24-26. Analyses were performed with an automated chemoluminescence immunoassay (IMMULITE®, DPC, CA, USA). Data are expressed as means with the 95% confidence intervals. sIL-2R levels at different time points were compared using the Mann-Whitney's U test. Multivariate linear regression analysis

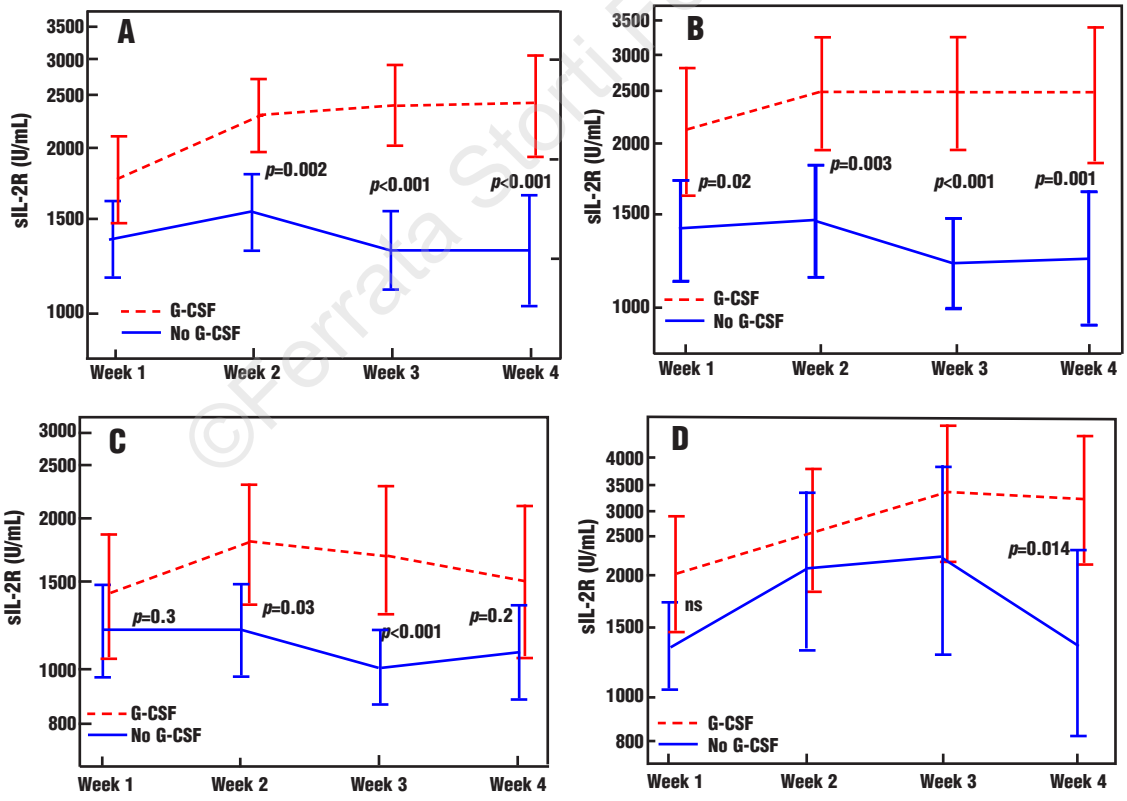

Figure 1. Serum levels of soluble IL-2 receptor (sIL-2R) in patients treated or not treated with G-CSF after allogeneic haematopoietic stem cell transplantation. A) All patients included. B) Only patients receiving a PBSC graft. C) Only patients without major complications (GVHD, vaso-occlusive disease, bacteremia). D) Only patients with acute GVHD grades II–IV. Data are expressed as means with a 95% confidence interval (CI). Differences for sIL-2R levels at different time-points were tested using Mann-Whitney's U test.

Table 1. Characteristics of 127 patients treated or not treated with G-CSF after HSCT. Absolute number or median and range.

	G-CSF N=57	*No G-CSF N=70*	*p*
Diagnosis			NS
Non-malignant disease	1	4	
Acute myeloid leukemia	25	22	
Acute lymphoid leukemia	11	10	
Chronic myeloid leukemia	9	12	
Myelo-dysplastic syndrome	5	8	
Other hematologic malignancy	5	9	
Solid tumor	1	6	
Disease stage (early/late)	36/20	26/38	0.01
Recipient gender (Male/Female)	38/19	43/27	NS
Recipient age	36 (1-62)	37 (0.5-64)	NS
Donor gender (M/F)	36/21	38/31	NS
Donor age	34 (3-67)	38 (3-71)	NS
Donor type			NS
HLA-identical sibling	26	23	
HLA-matched unrelated	31	47	
Stem-cell source (BM/PBSC)	24/33	21/49	NS
NC dose ($\times 10^8$/kg)	6.7 (0.8-38)	7.7 (0.6-64)	NS
Conditioning			0.04
Fractionated TBI+Cy	18	15	
Bu+Cy	29	30	
Fludarabine+Bu	5	16	
Fludarabine+TBI 2 Gy	1	0	
Fludarabine+Cy	4	9	
ATG (No/Yes)	22/35	17/53	NS

Early stage: malignancy in CR1 and non-malignant disorders, Late stage: all others, BM: bone marrow, PBSC: peripheral blood stem cells, NC: nucleated cell, TBI: total body irradiation, Cy: cyclophosphamide, Bu: busulfan, ATG: anti-thymocyte globulin.

was used in the analysis of prognostic factors for high sIL-2R levels. Factors included were G-CSF, GVHD, vaso-occlusive disease, bacteremia, type of conditioning, stem-cell source, donor, use of antithymocyte globulin and disease stage. The incidence of acute GVHD grades II–IV in patients treated or not treated with G-CSF was 29% and 14%, respectively (p=0.08). The time to neutrophil engraftment was significantly shortened by the use of G-CSF (median 16 days vs. 18 days, p=0.02), while platelet engraftment was delayed (24 days vs. 18 days, p=0.003). In ANOVA analysis, G-CSF-treated patients had higher levels of sIL-2R (p=0.02) than did non-treated patients (Figure 1A). This difference was mainly seen two (p=0.002), three (p<0.001) and four weeks (p<0.001) after HSCT. This has been reported previously.[7] A similar pattern was seen in patients receiving PBSC (Figure 1B). In the multivariate analysis (corrected for post-transplant complications, stem cell source, disease stage, donor type, type of transplant and antithymocyte globulin) we found that G-CSF was associated with increased levels of sIL-2R two and three weeks after HSCT (p=0.03 and p=0.01). Previous studies have shown that GVHD, vaso-occlusive disease of the liver and infections may lead to increased levels of sIL-2R.[5] We, therefore, analyzed patients without major complications. In this analysis we still found significantly higher levels of sIL-2R during G-CSF treatment two (p=0.03) and three (p<0.001) weeks after HSCT (Figure 1C).

In animal models it has been shown that G-CSF given to the donor, prior to the harvesting of stem-cells, directs the T cells towards a Th2 cytokine profile.[8,9] This shift towards a Th2 profile decreases the risk of GVHD. As donors are given G-CSF before the harvesting of PBSC, this has been taken as a reason for the unchanged risk of acute GVHD using PBSC compared to BM, even though ten times more T cells are administered. Furthermore, studies have shown that the risk of GVHD is reduced if the donor is treated with G-CSF before bone-marrow harvesting.[10] In patients with grades II-IV acute GVHD, significantly higher levels of sIL-2R were seen in G-CSF-treated patients at four weeks than in non-treated patients (Figure 1D). In a mouse model, interleukin (IL)-18 administration to donors produced a diminished Th1 response and an enhanced Th2 response after BMT, in contrast to an enhanced Th1 response after administration of the cytokine to the recipient. If introduced into a non-inflammatory environment, it directed the T cells into a Th2 profile, while if introduced into an inflammatory environment IL-18 directed the T cells into a Th1 profile. This may be the case with G-CSF as well. These and previous data[2,3] indicate that G-CSF should not be used as prophylaxis to enhance engraftment after HSCT. Even though G-CSF has been proven to shorten the neutropenic phase, it also extends the time to platelet engraftment. Therefore, G-CSF should probably be restricted to patients with threatening graft failure or other conditions in which it is of paramount importance to shorten the neutropenic period.

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Epidemiology

Newly diagnosed cases of hematologic malignancies in Sardinia in the early 2000s: an estimation of their number, age and geographic distribution on the basis of a previous epidemiologic survey

We estimate the number of cases of hematologic malignancies expected to be newly diagnosed in the resident population of Sardinia during the year 2001, and classify the predicted cases according to disease, age and geographic distribution. The implications of these predictions for the Sardinian health care system are discussed, particularly with respect to the development of policies aimed to ensure the most adequate medical care.

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In a previous report[1] we described age and sex distributions and temporal changes in the incidence of hematologic malignancies (HM) on the island of Sardinia during the years 1974-1993. Cases (in total 7,264) were collected by direct manual consultation of the registers containing all the reports of histologic examinations and the registers containing all the diagnoses at hospital discharge from, respectively, all pathology and clinical institutions active in Sardinia during that period; diagnoses were validated by consultation of clinical records, possible in 95% of cases. Pathologies classified as HM are those here reported in the Tables.

In this letter, we report an estimation of the number of HM expected to be newly diagnosed in the year 2001 in the resident population of the island and analyze the characteristics and geographic distribution of these malignancies. We also discuss some of the possible implications of these predictions for health care policy, in order to achieve the best management of these patients.

The number of cases was estimated by applying the HM incidence rates calculated from the survey mentioned above to the resident population of Sardinia at the 2001 census.[2] Details of the procedure applied are described in the legend to Table 1.

Table 1. Hematologic malignancies in Sardinia: estimated cases, 2001.

	Total cases	*>65 y*	*<15 y*
Acute myeloid leukemia	49	24	2
Acute lymphoblastic leukemia	23	5	8
Acute leukemia, unknown type	6	3	0.3
Myelodysplasia	46	36	0
Chronic myeloid leukemia	26	11	0.09
Polycytemia vera	11	5	0
Essential thrombocytemia	22	11	0
Myelofibrosis	9	6	0
Myeloproliferative disorders unknown type	3	3	0.03
Chronic lymphocytic leukemia	65	42	0
Multiple myeloma	66	40	0
Solitary plasmacytoma	1	0	0
Hodgkin's disease	45	7	1
Non Hodgkin's lymphomas	178	91	2
Hairy cell leukemia	7	2	0
Waldenström's macroglobulinemia	5	3	0
Lymphoproliferative disorders unknown type	4	2	0
Total cases	568	292	14

The number of expected cases was calculated by applying the specific incidence rates observed in our 1974-1993 survey[2] to the resident population of Sardinia at the 2001 census.[1] The rates applied are those of the whole surveyed period for diseases that had stable incidence rates (namely CML, ALL, HD) and those of the last 10 or 5 surveyed years for diseases incidence rates increased over time (mostly due to increased diagnostic efficiency). The number of cases could be higher than estimated for NHL, AML and MDS, whose rates increased over the entire period covered by our previous survey.

The same calculations were applied uniformly across the three areas into which we had arbitrarily divided the island. This division was made on a logistic basis i.e. road access to Cagliari, Sassari and Nuoro, the towns where the four hematology institutions most extensively involved in HM care are located. This division was documented to be reliable when retrospectively checked on the patients of the 1974-1993 survey. Details of the procedures applied are described in the legend to Table 2.

Based on our analysis, the number of new HM cases expected to be diagnosed across the whole Sardinian population (1.631.880 at 2001 census) in the 2001 would be 568 (this could be an underestimate, as explained in the legend to Table 1). Table 1 shows the estimated division of these cases by disease and by two particular age classes (i.e.<15 and >65 years of age respectively). The estimated number of patients under 15 years old is only fourteen, with about twenty in total under 18 years old. Patients over 65 years old are expected to represent more than 50% of the total HM cases (292/568). Co-morbidity typical of this age group still further increase the burden on the health care system and must be taken into account when considering an adequate training of hematology staff.