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Joint Accreditation Committee of the International Society for Cellular Therapy and the European Group for Blood and Marrow Transplantation accreditation for autologous hematopoietic stem cell transplantation in non-leukemic malignancies: burden or benefit?

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Autologous hematopoietic stem cell transplantation (HSCT) is considered to be a high-risk procedure and requires the cooperation of many health care professionals. Because of that, a special quality management system 'Joint Accreditation Committee of the International Society for Cellular Therapy and the European Group for Blood and Marrow Transplantation (JACIE)'was implemented in the hope to improve patient care and outcome [1]. In the Netherlands, this system is mandatory for all hospitals performing autologous and allogeneic HSCT. This special quality management system requires among many other things special training for all physicians and nurses involved, special isolation measures, extensive description of standard operating procedures and a strict documentation of the bone marrow recovery in every transplanted patient.[1] According to our opinion, the complications and complexity of an autologous HSCT in patients with non-acute leukemic malignancies do not differ so much from daily hemato-oncological care that an apart qualification system contributes to the improvement in the outcome of these patients. Indeed, Gratwohl et al found that the JACIE accreditation had no impact upon the outcome of patients undergoing autologous HSCT [2].

Patients undergoing HSCT are often characterised as high risk patients with an expected duration of neutropenia > 7 days [3]. The underlying diagnosis, the extent of pre-treatment, the amount of reinfused peripheral stem cells and the conditioning regimen before stem cell transplantation have impact upon the duration of neutropenia and other toxicities [3-9] Infections are the most frequent complications in HSCT patients, influenced by the depth and duration of neutropenia and the extent of mucositis [10].

We performed a retrospective study in all patients who underwent an autologous HSCT from 2008-2012 in our institute to investigate the relationship between the absolute duration of neutropenia in relation to the malignancy, the occurrence of neutropenic fever, mucositis and other toxicities. Based on these results, we wish to start a debate if a special time consuming and costly accreditation system and the special measures mandatory to achieve the accreditation are really warranted for the clinical part of autologous HSCT in non-acute leukemic malignancies. Since we do not treat patients with acute leukaemia's in our hospital, this patient category was not represented in this study.

All patients had given informed consent for high dose treatment and medical record review. We (SH, JWB) reviewed all records of the patients treated with high dose chemotherapy followed by an autologous stem cell transplantation. The collected parameters were: age, sex, performance status, comorbidity, diagnosis, treatment before the stem cell transplantation, the amount of CD34+ cells/kg body weight reinfused, type of conditioning regimens before transplantation, duration of absolute neutropenia after the stem cell transplantation, occurrence of fever, culture of causative micro-organisms, mucositis, other side effects of the high dose treatment.

The high dose chemotherapy regimens administered were: BCNU 300 mg/m^2 during 1 day, etoposide and cytarabine both 200 mg/m^2/day during 4 days, Melphalan 140 mg/m^2 during 1 day (BEAM) for patients with malignant lymphoma; high dose Melphalan (HDM) 100 mg/m^2/day during 2 days for patients with multiple myeloma; cyclophosphamide 1500 mg/m^2 /day , carboplatin 5 x area under curve (AUC)/day , thiotepa twice daily 60 mg/m^2 all agents for 4 consecutive days (CTC) for patients with testicular cancer and medulloblastoma; mini CTC for patients with breast cancer: cyclophosphamide 3000 mg/m^2 during 1 day, carboplatin 400 mg/m^2 (in case of creatinine clearance < 100 ml/min: 5 x AUC) during 2 days and thiotepa 250 mg/m^2 during 1 day. The patients with testicular cancer, medulloblastoma and breast cancer received two transplantations with the same regimen. All patients received G-CSF (filgastrim) 300 micrograms a day, started one day after the reinfusion until neutrophilic cell count reached 1000 x 10^6 cells/ml or until the absolute neutrophil count exceeded >500 x 10^6 cells/ml for 2 consecutive days.

All patients received prophylactic antibiotics according to local

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guidelines and based on routine cultures taken twice weekly. When fever occurred, broad spectrum antibiotics were started and multiple samples of blood cultures, urine, sputum and specimens from suspected sites were taken to identify the causing micro-organism. In case of allergy or specific culture results, other antibiotics were administered.

Absolute neutropenia was defined as a neutrophil count of < 500 x 10^6 cells/ml. Neutrophil engraftment was defined as the first day on which the absolute neutrophil count (ANC) exceeded >500 x 10^6 cells/ml for 2 consecutive days.

The transfusion threshold for irradiated erythrocytes was hemoglobine < 6g/dl and for irradiated pool platelets a platelet count <10.000/microl.

The patients received standard anti-emetic care.

Mucositis grades were defined according to the common terminology criteria for adverse events (CTCAE) version 4.0 as were the other toxicities.

Fever was defined as a single ear or oral temperature measurement of ≥ 38.5 degrees Celsius or ≥ 38 degrees Celsius over 1 hour period.

The cohort consisted of 86 patients of which 65 patients received a single- and 21 a double transplantation, 107 HSCT in total. Apart from the remission-induction treatment and chemotherapy for stem cell mobilisation, almost half of the patients received their HSCT as part of their salvage therapy for relapse. 25 patients (29%) received one line of pre-treatment and 13 (15%) received two lines (Table 1).

Seven (8%) patients experienced a prolonged neutropenia (ANC < 500 x 10^6/ml > 7 days). In eight procedures (7.5%) a prolonged neutropenia occurred. The patient- and treatment characteristics are shown in table 1.

Four patients with duration of neutropenia > 7 days were pre-treated with at least 2 lines of chemotherapy, 2 patients with breast carcinoma had no prior treatment. One patient with multiple myeloma had received the second autologous stem cell transplantation 4 years after the first one (Table 1).

Table 2 shows the duration of neutropenia and hospital stay, the number of harvested and reinfused peripheral stem cells, mucositis, occurrence of fever, the median number of transfused unit's erythrocytes and pools thrombocytes. No grade 3 or 4 transfusion- or stem cell reinfusion related toxicities occurred. In total 59 episodes of fever were observed. In half of the cases, micro-organisms were cultured, the most frequent coagulase negative staphylococci. All 4 candida albicans infections were limited to oropharyngeal infections. 6 patients had a grade III/IV mucositis. 4/6 of these patients had a duration of neutropenia > 7 days. All 6 patients developed neutropenic fever (Table 3).

No grade III, IV organ or lethal toxicities took place during the HSCT. There was no difference in toxicities between the first or second HSCT. All patients had full bone marrow recovery.

Twelve of the 86 patients were treated with radiotherapy, but in none of these patients a significant part of the bone marrow was located in the radiation field.

Our study shows that only 8% of our patients undergoing autologous HSCT had an absolute duration of neutropenia (< 0.5 x 10^9/l) > 7 days and 7% of the patients had a mucositis grade ≥ 3 (Table 2-3). All toxicities, also in the patients with a prolonged duration of neutropenia, were manageable with standard hemato-oncological care. The pattern of bone marrow recovery is stable over years (Table 2).

The relative short duration of neutropenia in the majority of patients does not warrant strict isolation. Patients can be nursed in a normal ward or stay at home with regular outpatient clinic controls. Instead of making a file in which the bone marrow recovery is 'exactly' documented (results also depending on how frequently blood is taken for laboratory control), one can consider to look which percentage of patients is recovered 14 days after the autologous HSCT in terms of transfusion independency, recovery from non-hematologic acute toxicities and the ANC being > 1000 x 10^6/ml. This is less time consuming and burdensome for patients and personnel than counting the days before bone marrow recovery takes place.

It is known that centre size and experience of the medical personal

Table 1. Baseline characteristics.

	Total population Number (%)
Sex	
Men	49 (68)
Women	37 (32)
Age (years)	
Median	46
Range	21-72
Diagnosis	
Medulloblastoma	1 (1)
Breast cancer	30 (35)
Multiple myeloma	20 (23)
Non-Hodgkin lymphoma	15 (18)
Hodgkin lymphoma	13 (15)
Non-seminoma testis	7 (8)
Conditioning regimes	
CTC	8 (9)
mCTC	30 (35)
BEAM	28 (33)
High dose Melphalan	20 (23)
Transplantations	
1 transplantation	65 (76)
2 transplantations	21 (24)
Chemotherapy pre-treatment	
No pre-treatment	48 (56)
One line	25 (29)
Two lines	13 (15)

Table 2. Main toxicities, stem cell harvest and hematologic recovery of 86 patients after HSCT.

	Median	Range
Reinfusion		
Harvested CD34+ cells x 10^6/kg	8.0	2.6-88.0
Reinfused CD34+ cells x 10^6/kg	4.9	1.8-11.5
Bone marrow recovery		
Duration of ANC < 500 x 10^6/mL (days)	4.0	2.0-15.0
Leucocytes > 500 x 10^6/mL after HSCT in days	9.0	8.0-14.0
Thrombocytes > 10.000 /microL after HSCT in days	9.0	6.0-14.0
Thrombocytes > 20.000 /microL after HSCT in days	10.0	6.0-25.0
Thrombocytes > 50.000 /microL after HSCT in days	16.0	7.0-36.0
Supportive care		
Number of transfused filtrated erythrocytes	2.0	0.0-7.0
Number of pooled thrombocytes	2.0	0.0-13.0
Duration of hospital stay (days)	16.0	4.0-40.0

Table 3. Toxicities: Fever and mucositis.

Fever	Number (%)
Fever	59 (69)
No fever	27 (31)
Mucositis grades (whole population)	
No	23 (27)
Grades I and II	57 (66)
Grades III and IV	6 (7)
Mucositis grades and infections	
No mucositis	12 (26)
Mucositis gr I and II	29 (62)
Mucositis gr III and IV	6 (12)

with intensive oncological treatments have impact on the outcome of the patients[2]. The centre has to perform enough procedures per year (≥10/year) with a stable senior staff to guarantee good quality of patient care. The authorities have to make demands on the number of patients transplanted each year in a specific hospital. In addition, accreditation systems should be short and comprehensive. The current 473 pages JACIE manual trying to regulate each detail and trying to avoid very rare complications is hardly readable anymore, puts a burden on the medical personnel, quality officers and does not contribute to the improvement of patient care and safety [1,2].

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