Proffered papers

BMT and PSCT

1118 ORAL

AMIFOSTINE IMPROVES THE ANTILEUKEMIC THERAPEUTIC INDEX OF MAFOSFAMIDE: IMPLICATIONS FOR BONE MARROW PURGING

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To test the potential use of amifostine (Ami) to protect normal bone marrow (N1 BM) progenitor cells during ex vivo purging of leukemia, the dose response of mafosfamide (Mfs) ± Ami on N1 BM progenitor cells was determined and the LD_{95} was calculated. Ami pretreatment resulted in a statistically significant protection of CFU-GM and erythroid blast-forming units (BFU-E) from Mfs toxicity. The mean ± SEM μg/ml LD_{95} concentrations were: CFU-GM, Mfs alone 54 ± 13 vs Ami-Mfs 66 ± 14, p .005, BFU-E, Mfs alone 48 ± 14, vs Ami-Mfs 61 ± 11, p .005. In contrast, Ami pretreatment sensitized CFU-L to Mfs toxicity: LD_{95} for Mfs alone 33 ± 4 vs Ami-Mfs 27 ± 3, p .003. At the LD_{95} for CFU-GM and BFU-E, Mfs alone resulted in a ≈4 log cell-kill for L-CFU. Ami protection of N1 BM resulting in a higher Mfs LD_{95} concentration, coupled with the Ami-sensitization of the leukemia, provided an estimated additional 6+ log leukemia cell-kill. This enhanced selective leukemia cell-kill from Mfs during ex vivo purging using the LD_{95} concentration of Mfs for normal marrow progenitors offers the potential for lowering the incidence of leukemic relapse while preserving a greater number of normal progenitor cells for engraftment following autologous transplantation.

1119 ORAL

GLYCYL-GLUTAMINE SUPPLEMENTION AND HIGH DOSE THERAPY

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The amino acid, l-glutamine is the major energy substrate of the intestinal epithelium. Dietary supplementation reduces GI toxicity after RT and CT in animal models. The maximal insult to the gut occurs during high dose conditioning therapy and in this study glycyl-l-glutamine (GLG) supplementation is commenced one day before high dose therapy starts. *In vitro* testing showed minimal shifts in chemo or radiosensitivity with glutamine supplementation. This double blind randomised trial compares 50 g/day GLG iv supplementation versus an isonitrogenous mixture of aminoacids. Serum glutamine concs were doubled from a mean of 398 at baseline to 812 μmolar at end of infusion.

	GLG (19)	Placebo (12)
Median days to 0.5 neutrophils	14	16
Median days to 50 platelets	18	21
Median hospital stay post graft	19 (12–44)	22 (14–48)
Mucositis score (nurse)	3.1	7.5

These results suggest a beneficial effect of GLG supplementation on gastrointestinal toxicity and haematological recovery with reduction in hospital stay and warrant further study.

1120 ORAL

FACTORS THAT INFLUENCE PERIPHERAL BLOOD STEM CELL HARVEST AFTER HIGH-DOSE CYCLOPHOSPHAMIDE AND CARBOPLATIN FOLLOWED BY GM-CSF INFUSION

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The peripheral blood stem cell (PBSC) mobilization capacity of carboplatin (CBDCA, 800 mg/m^2) followed by GM-CSF infusion (5 μg/kg) is being compared with that of cyclophosphamide (CTX, 7 g/m^2) followed by the same dose of GM-CSF. So far, 18 patients, 5 MM, 9 LG-NHL, 4 HD, have been entered in the study. PBSC were not collected after CBDCA in 4 cases, one due to early discharge, one because of suspected, but unconfirmed, allergy to GM-CSF, one because the CBDCA dose was reduced to 400 mg/m^2, one because G-CSF was substituted for GM-CSF due to hypotension and dyspnea, which, however reappeared 3 times while patient was off treatment. 53 stemophereses were analyzed in the other 14 patients after CTX and 43 after CBDCA for a mean of 6.8 /patient. Mean CFU-GM × 10^6/l recovered were 0.34 ± 0.2 after CBDCA and 0.58 ± 0.78 after CTX (P = NS). Mean CD34+ × 10^6/l were 35.9 ± 118 after CBDCA and 24 ± 34.4 after CTX (P = .00034). Multifactorial analysis performed to identify the variables that influence CFU-GM × 106/l and CD34+ × 106/l recovery revealed that the relevant factors for CFU-GM were: the CFU-GM/ml, the percentage and absolute values of CD34+ /ml in the peripheral blood the day stemopheresis was effected, the type of disease, the number of bone marrow CFU-GM before starting therapy (bone-marrow proliferations). For CD34+ they were: the WBC/l, the percentage and absolute values of CD34+/ml present on the day of stemopheresis, the type of disease and the bone-marrow proliferation before starting therapy.

1121 ORAL

DNA SYNTHESIS OF PROLIFERATING SUBPOPULATIONS OF HUMAN BONE MARROW INCLUDING CD34+ CELLS ALONG THE CIRCADIAN TIME SCALE

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We have extended earlier flow cytometric circadian studies of total bone marrow (BM) cells to also include proliferating BM subpopulations (i.e., myeloid lineage, erythroid lineage, CD34+ cells) with the intent to further optimize cancer chromotherapy with chemotherapeutics or cytokines, taking into account temporal susceptibility rhythms of critical BM cell populations. BM was aspirated at 5 hour intervals from the sternum and iliac crests from 5 healthy men, aged 23–26 years, altogether 5 times during a 24 hour time span. To separate the myeloid, erythroid and lymphoid subpopulations indirect immunostaining was performed with the common leukocyte antigen CD45, and the myelomonocytic marker CDw65 (VIM2). The most proliferating myelomonocytic cells (VIM prol.) could further be separated from the rest of the myelomonocytic cells. Isolation of CD34+ cells was performed by a technique using immunomagnetic beads coated with the anti CD34 monoclonal antibody BI-3C5. Subsequent DNA staining was performed with a hypotonic propidium iodide solution. The circadian variation in S-phase for total proliferative BM cells was found in 4 of 5 subjects to be the same as earlier reported (i.e., high S-phase during day and low during evening or night; Blood 77: 2603–11, 1991). The most proliferating myelomonocytic cells also demonstrated higher S-phase during day as compared to night (P = 0.0198; Mann-Whitney U) with a mean S-phase of 14.2% ± 3.5.% (S.D.). The circadian variation of the CD34+ S-phase cells corresponded to the circadian pattern of the VIM prol. cells in 3 of 5 subjects;

however, the amplitude was less pronounced. Mean CD34+ S-phase was 14.0% ± 1.7% (S.D.). Interindividual differences in circadian variation in the S-phase of erythroid cells were observed. Therefore, no significant variation was demonstrated for the pooled S-phase of these cells, which had a high mean S-phase of 25.4% ± 2.7% (S.D.).

1122 ORAL

FACTORS AFFECTING ADEQUACY OF SINGLE VS MULTIPLE APHERESIS FOR STEM CELL COLLECTION DURING MOBILIZATION FOR RESCUING PATIENTS AFTER HIGH DOSE CHEMOTHERAPY

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Thirty nine pts with malignancy were enrolled in a study of high dose chemotherapy and peripheral blood stem cell transplantation (PBSCT). Stem cells were harvested prior to PBSCT using (1) G-CSF 10 μg/Ug/d (2) high dose cytoxan 6 gr/m^2 (H.D CTX) + G-CSF (3) conventional chemo (C.CHE) + G-CSF or GM-CSF (4) G-CSF + GM-CSF with collection of a median of 4.3 × 10^8/kg MNC (range 0.56–10.1) and 16.8 × 10^4/kg CFU-GM (range 1.8–55.2). Seven pts required more than a single apheresis and 10 pts (26%) didn't reach the optimum CFU-GM target (>10 × 10^8/kg) following the mobilization. Method of mobilization, nature of disease, age, BM infiltration, number of chemo cycles and RT premobolization, time of last chemo to mobilization were the factors been studied for the effect on blood stem cell collection. The factors identified those pts who achieved optimum CFU-GM collection included the lower number (<9) of chemo cycles and no extensive RT premobilization (Table I).

	Median no chemo cycles premobilization (days)			Premobilization RT	
	⩽6	6 ⩽ 9	>9	yes	no
Median total MNC harvested (×10^8/kg)	4.3	6.11	2.73	1.81	4.85
Median total CFU-GM harvested (×10^4/kg)	15.9	24.2	8.5	3.74	19.65

Mobilization method, age, BM infiltration, disease and interval from last chemo cycle to mobilization did not affect the ability to collect CFU-GM numbers. Refinement to the protocol, in particular the use of growth factors, are currently under investigation.

1123 ORAL

ABLATIVE CHEMOTHERAPY AND BMT/PSCT IN EARLY RELAPSING OR MULTIFOCAL EWING SARCOMA. THE VALUE OF RADIOTHERAPY

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Introduction: The fate of patients with early recurring or multifocal Ewing sarcoma is poor. Patients who relapse within the first 2 years have a 5 year event free survival probability of 2% (CESS 81). The prognosis drops down to a 5 year free survival probability of 0% (CESS 81) for patients with multifocal bone lesions. This poor prognostic Ewing sarcoma group was defined as eligible for ablative radio-chemotherapy and BMT/PSCT in first complete remission.

Materials and Method: Within the EICESS group 63 patients have been treated since 1987, 24 of them in Düsseldorf. All patients underwent remission induction chemotherapy with 4 courses (EVAIA) and 2 courses EVAIA simultaneously to hyperfractioned consolidation radiotherapy of all detectable involved compartments. The delivered target dose was 43.2 Gy (55 Gy including 12 Gy TBI), fractionated in 2 × 1.6 Gy/day up to 22.4 Gy simultaneously to the 5th and 20.8 Gy to the 6th EVAIA course. Dose reduction was required to tissue tolerances. After clinical and histological proven CR patients underwent high dose chemotherapy (melphalan and etoposide) and TBI with a total dose of 12 Gy (2 × 1.5 Gy) during day −7 to day −3. Lungs were shielded at 8 Gy in the beginning and later at 10 Gy followed by a rip cast boost to 12 Gy.

Results: 22/63 patient (35%) in the whole group and 10/23 pts. (43.5%) in Düsseldorf are alive. 13/23 pts. (56.5%) in Düsseldorf (3 DOC, 10 DOD). Due to multifocal bone lesions huge bone marrow volume have to be irradiated (7% to 48%, average 18%). Under the cover of G-CSF engraftment for WBC was on average 12.7 days (8–25), erythrocyte dependency on average 52 days (13 > 200) and thrombocyte dependency on average 50 days (12 > 200).

Conclusion: Myeloablative radio-chemotherapy with BMT/PSCT improves the prognosis of poor prognostic Ewing sarcoma. Tumour control still remains the main problem. Extensive radiotherapy of bone marrow immediately before BMT/PSCT does not lead to delay of WBC engraftment.

1124 ORAL

EVALUATION OF PATHOLOGICAL RESPONSE FOR BREAST CANCER AFTER HIGH DOSE CHEMOTHERAPY (HDC) AND AUTOLOGOUS STEM CELL SUPPORT

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Between 1981 and 1993, 20 of the 101 pts treated by HDC for breast cancer had mastectomy post treatment. 10 were treated for an inflammatory and 10 for a poor prognosis breast cancer. All of them received prior HDC an anthracyclin based chemotherapy. The overall clinical response rate to HDC was 90% (15/20 CR, 3/20 PR). 1 was in SD and 1 NE. 35% (7/20) were in pathological CR, all of them were in clinical CR. With the median follow-up of 23 [6–78] months 30% (6/20) relapse, 4 of them were in clinical CR post HDC, 1 in RP and 1 NE. Any of them were in pathological CR. Pts who received first conventional chemotherapy and HDC have 35% pathological CR. With more pts and longer follow-up, we want to define more precisely the clinical and pathological response to HDC. Actually, these results show us that it necessary to associated a local treatment to a systemic chemotherapy for high risk primary breast cancer.

1125 ORAL

HIGH-DOSE THERAPY WITH HEMOPOIETIC STEM CELL SUPPORT FOR HIGH RISK BREAST CANCER. A PILOT STUDY IN 31 PATIENTS

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From February 1992 to August 1994 31 women with high risk breast cancer received high dose cyclophosphamide (1.5 g/m^2 × 4 days), carboplatin (200 mg/m^2 × 4 days continuous infusion) and thiotepa (125 mg/m^2/4 days, continuous infusion) as intensification treatment after conventional adjuvant chemotherapy. Median age was 43 years (27–61). Bone marrow was employed as source of stem-cell support in 22 patients and G-CSF mobilized peripheral stem cell in the rest 9 patients. G-CSF as a dose of 5 mcg/kg/day was administered in all bone marrow transplant patients until neutrophil engraftment. No toxic death occurred and major toxicities were as follows: neutropenic fever (31/31), grade II and III mucositis (5), grade II and III gastrointestinal toxicity (6), mild hemorrhagic cystitis (2), pulmonary embolism (1), post-transfusional hepatitis (1), grade II cardiac toxicity (1), pulmonary hemorrhage (1). Median days to reach neutrophil (>500/mm^3) and platelet engraftment (> 25000) were 12 (9–30) and 18 (9–34) respectively. Median days of hospitalization were 24 (19–42), and for intravenous antibiotics 12 days (5–23). Red packed cells and platelets requirements were 4 (0–7) and 42 (6–141) respectively. There were no difference in terms of engraftment, days of antibiotics, transfusion requirements, use of antifungal therapy, time of hospitalization between patients that received bone marrow or peripheral blood stem cells as blood support. Nevertheless a trend for a lower value in all these variables was observed for peripheral stem cell. With a median follow-up of 12 months (3–31) four patients relapsed on days 113, 206, 248, 374 after transplant. Disease-free survival at 2 years is 72%. Three out of four relapsed patients died. Multiple metastatic sites at relapse occurred in 3 patients (liver: 2, skin: 1, pleural 2, pulmonary 2, nodes: 1). A poor response to salvage chemotherapy with a rapid progression and death occurred in three patients.