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PREVENTIVE VERSUS THERAPEUTIC USE OF G-CSF FOLLOWING HIGH DOSE CYCLOPHOSPHAMIDE (H.D.CTX)

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The preventive vs therapeutic administration schedules of G-CSF is under study in this trial. Thirty-eight patients with advanced malignancies received CTX 4.5 gr/m^2 and equal dose of Mesna divided in two days. The pts were randomized to receive G-CSF 5 μg/kg/d s.c. on five schedules: (1) Control group without G-CSF, (2) Group A: 24 h after the end of H.D.CTX, (3) Group B: 48 h, (4) Group C: 72 h, (5) Group D: 96 h, (6) Group E: when WBC < 1000/μl. To date 38 pts and 67 cycles were evaluable. The median age was 52 years, 28 were women and 10 men ECOG PS 0–3 and all patients had received prior chemotherapy

	Control	A (24h)	B (48h)	C (72h)	D (96h)	E (WBC < 1000)
No of courses	**10**	**12**	**11**	**12**	**12**	**10**
Median duration of neutropenia < 500/μl	10	4	4	5	5	5.5
Median neutrophil nadir	100	200	150	100	180	100
Median duration of lebrile days with neutropenia	4	0	0	0	2	4
Incidence of neutropenia with fever > 38°C (% of courses)	10%	16%	27.5%	27.5%	66%	80%
Onset of neutropenia	8	8	7	9	8	8
Duration of G-CSF administration	-	12	11	10	8	8.5

(1) There is no significant difference among the groups in onset, in duration of neutropenia and neutrophil nadir. (2) Pts of 24, 48, 72 h had statistically less febrile days with neutropenia when compared with controls, 96 h and of WBC < 1000 μl. These data suggest that the timing of G-CSF administration does not affect the duration of neutropenia and neutrophil nadir. Although the cost of G-CSF administration decreases significantly when administered therapeutically, preventive administration up to 72 h is indicated.

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A PHASE II STUDY OF THE RECOMBINANT HUMAN INTERLEUKIN 3 (IL-3) FOLLOWING CARBOPLATIN (CBDCA) AND ETOPOSIDE (VP-16) CHEMOTHERAPY IN PATIENTS WITH SMALL CELL LUNG CANCER (SCLC)

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To evaluate the safety and the efficacy of IL-3 (Sandoz), SCLC patients (pts) received a subcutaneous infusion of IL-3 for consecutive 10 days. The chemotherapy was consisted of CBDCA (400 mg/m^2 for previously untreated pts or 350 mg/m^2 for previously treated pts on day 1) and VP-16 (100 mg^2 on days 1–3) every four weeks. If the nadir of platelet counts was < 75 × 10^3/ml in the observation cycle of chemotherapy, pts were randomly assigned for the next cycle to either 5 or 10 μg/kg/day of IL-3, administered on days 4–13 (28 pts, median age 67 years). The nadir of platelet counts were 42 × 10^3/ml in the observation and 62 × 10^3/ml in the IL-3 cycle ($P < 0.001$). Recovery of platelet counts > 100 × 10^3/ml was faster in the IL-3 cycle (17 days) than the observation cycle (21 days: $P < 0.001$). Grade I/II fever was most frequently observed (79%). There were no grade III/IV IL-3 related adverse events. **In conclusion,** the IL-3 infusion following the CBDCA and VP-16 chemotherapy appears to reduce chemotherapy induced-thrombocytopenia with an acceptable toxicity.

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GM-CSF INDUCED ACTIVATION OF T-LYMPHOCYTES AND MACROPHAGES

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The effect of GM-CSF infused after 7 g/m^2 cyclophosphamide (CTX) and 800 mg/m^2 carboplatinum (CBDCA) was evaluated in 16 (LG-NHL, MM, HD) patients. Serum concentrations of soluble CD8 (sCD8) and soluble IL-2 receptor (sIL-2R) as well as circulating levels of IL-2, IFN-γ, neopterin, IL-1α, IL1-β, TNF-α and IL-6 were determined on day 0 and days +4, +10 and +16 post-GM-CSF and intracellular IL-2, IFN-γ, IL-1α, IL-1β, TNF-α and IL-6 on days 0 and +16. sIL-2 R rose from day +4 to day +16 and reached twice basal values at 10 and 16 days after both CTX (2266 ± 904, 2292 ± 873 vs 1189 ± 608) and CBDCA (2225 ± 965, 2313 ± 1055 vs 1151 ± 518). Neopterin also rose and was maximum on day +16 (1.7 post-CTX, 1.6 post-CBDCA vs basal). Serum IL-1α concentrations varied little after CTX, but increased two-fold over basal values after CBDCA (39.3 ± 34.6 vs 15.8 ± 40.5). Serum IL-1β increased 1.3 on the 16th post-GM-CSF day after CTX and 1.8 after CBDCA. Serum TNF-α rose to 1.8 basal values on day +10 and to 3.5 on day +16 following CBDCA, but not after CTX. Changes in the other serum and intracellular indices studied were negligible. These results suggest that GM-CSF activates T-lymphocytes and macrophages, but that their activation partially depends on the therapy that precedes administration of the growth factor.

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AMIFOSTINE STIMULATES HEMATOPOIETIC PROGENITORS FROM HUMAN NORMAL AND MYELODYSPLASTIC (MDS) BONE MARROWS

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Studies have demonstrated the trilineage hemoprotective effects of amifostine (Ami). Recent studies suggested direct stimulation of hematopoiesis. *In vitro* growth of CFU-GEMM, BFU-E and CFU-GM from normal and MDS bone marrows was evaluated after 15 min preincubation with Ami or its active metabolite, WR-1065, glutathione (GSH), or recombinant growth factors. Concentrations of Ami and WR-1065 at 0.1–1000 μM stimulated growth of CFU-GEMM and BFU-E from normal marrow mononuclear cells; >10 μM GSH was toxic. Ami was the most potent stimulant yielding up to 9-fold greater BFU-E, 4× CFU-GEMM and 3× CFU-GM over controls. Compared to kit ligand, IL-1 and IL-3 (200 U/ml), Ami was a more potent hemopoietin yielding up to 3× greater CFU-GEMM and BFU-E recovery. Despite deficient colony growth in MDS controls, Ami preincubation with clinically achievable concentrations (100–500 μM) stimulated growth of CFU-GEMM and BFU-E 2–7-fold and improved colony/cluster ratio in 7 of 8 pts studied. The data indicate that Ami is a potent stimulant of primitive progenitor growth that exceeds that of recombinant cytokines. The profound simulation observed in MDS suggests that Ami may improve hematopoiesis in patients with MDS and warrants testing in clinical trials.

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COMPARISON OF TWO STEM CELL MOBILIZATION AND HARVESTING REGIMENS FOR PERIPHERAL BLOOD STEM CELL (PBSC) TRANSPLANTATION IN MULTIPLE MYELOMA (MM)

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We have investigated two regimens for the mobilisation of stem cells prior to PBSC transplantation in MM. Regiman A: 125 μg/m^2 GCSF b.d. for 7 days with harvest of stem cells days 5–8. Regimen B: 12–16 μg/kg for 4 days with harvest days 4 and 5. For each regimen the median total cell count, CFU-GM and CD34 + counts and days to engraftment as measured by time to attainment of neutrophil count 500 were calculated and compared by the Mann-Whitney non-parametric test.

Results:

	A (n = 25)	B (n = 13)	Mann-Whitney p value
Total cell count ($\times 10^8$)	6.6 (4.05–12.18)	4.06 (30–7.72)	0.0002
CFU-GM ($\times 10^4$/kg)	3.14 (0.44–24.5)	3.35 (0.06–21.27)	NS
CD34+ ($\times 10^6$)	43.6 (0.3–337.7)	38.5 (4.1–1187.7)	NS
Days to engraftment	12 (6–21)	12 (8–23)	NS

Conclusions: Although Regimen A led to increased mononuclear cell count there was no difference in the CFU-GM or CD34+ counts or days to engraftment. Reduction of stem cell harvest time from 4 to 2 days has economic benefits and improves patient tolerability.

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A PHASE III TRIAL OF RECOMBINANT GRANULOCYTE-MACROPHAGE COLONY STIMULATING FACTOR (GM-CSF) AS CORRECTIVE TREATMENT IN PATIENTS (PTS) WITH NEUTROPENIC FEVER FOLLOWING ANTINEOPLASTIC CHEMOTHERAPY (CT): RESULTS OF AN INTERMEDIATE ANALYSIS

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Fifty-one patients (pts) with neutropenic fever (fever $\geqslant 38.5°$ C at 3 hour-interval and an absolute neutrophil count (ANC) $< 1.10^9$/l) following chemotherapy have been included. All had a non-myeloid tumor and an ECOG performance status $\leqslant 2$ at the beginning of the last CT course. None had received G or GM-CSF as prophylactic treatment nor prophylactic antibiotherapy or glucosteroids during the last 10 days.

Patients were hospitalized and randomized, in the 12 hours following the beginning of fever, to receive either IV antibiotherapy (control group) or antibiotherapy and GM-CSF, given subcutaneously at a daily dose of 5 μg/kg, to be continued until 2 days after the recovery of ANC $\geqslant 1.10^9$/l. A stratification was done, before randomization, according to chemotherapy level of hematologic toxicity [i.e.: high (HCT) versus moderate (MCT)]. There were 19 male and 32 female, with a median age of 50.8 years old (18–79). Twenty-five pts had received HCT and 26 MCT. Results are summarized in the table below:

Treatment arm	**GM-CSF**	**Control group**	**Wilcoxon's test (p)**
number of pts	26	25	
median days with ANC $< 0.5\times10^9$/l (range)	3 (1–8)	4 (1–9)	0.06
median days with ANC $< 1\times10^9$/l (range)	3 (1–10)	6 (2–12)	<0.001
median days with ANC $< 0.5\times10^9$/l, HCT pts (range)	3 (1–18)	4 (1–6)	0.66
median days with ANC $< 1\times10^9$/l, HCT pts (range)	4 (1–10)	5 (2–12)	0.22
median days with ANC $< 0.5\times10^9$/l, MCT pts (range)	2 (1–4)	4 (1–9)	0.04
median days with ANC $< 1\times10^9$/l, MCT pts (range)	3 (1–5)	7 (2–10)	<0.001
median days with fever $\geqslant 38.5°$	2.5 (1–7)	2 (1–12)	0.39

One pt, in the control group, died with infection. Side effects related to GM-CSF consisted in mild bone pain in 2 pts. In conclusion, GM-CSF, given as corrective treatment, significantly reduced the duration of neutropenia (days with ANC $< 1\times10^9$/l) following chemotherapy. At time of analysis, this effect appeared more pronounced after moderately hematotoxic chemotherapy rather than after highly hematotoxic chemotherapy. These results will be updated for presentation.

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GROWTH FACTORS IN COMBINATION: PHASE I STUDY OF DOSE INTENSIFIED CARBOPLATIN (CB), CYCLOPHOSPHAMIDE (CT) AND ETOPOSIDE (VP) IN PATIENTS (PTS) WITH ADVANCED, REFRACTORY CANCER

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This phase I study was designed in order to verify the toxicity of CB. CTX, VP given at high doses, in combination with GCSF alone or GCS and GMCSF given sequentially. The two lymphokines, with different properties, might have their ideal integration in the sequential administration. A group of 10 heavily pretread patients (PTS) with stage IV disease (2 breast cancer, 2 small cell and 1 non small cell lung cancer, 1 sarcoma, 1 colorectal cancer, 1 ependymoblastoma, 1 signet-ring cell bladder cancer, 1 neuroendocrine prostate cancer) were enrolled into the study between August and September 1994. Median (M) PS (ECOG) was 1, M age 41 years (22–65). Previous treatments: 7 PTS had surgery, 4 PTS had radiotherapy, all PTS had received previously a median of 4.5 chemotherapy courses (4–12). CB-CTX-VP combination was administered over 3 days. Each patient, received two courses of the same CT, followed, randomly, either by 14 days of GCSF (arm A) or by 7 days of GCSF and 7 days of GMCSF (arm B) with cross over in the second CT course. Both growth factors were given sq at the dose of 5 μg/kg/day. CB dose was calculated according to Calvert *et al.* (*JCO* 1989, **7:1748**) and expressed with the area under the concentration versus time curve (AUC). All patients received an outpatient treatment. The maximum tolerated doses of CTX and VP, found in a previous work (*Ann Oncol* 1994, **5:90,**), were, respectively, 1500 and 400 mg/m^2, while CB doses ranged from 5 to 8 AUC. Twenty chemotherapy courses over 20 are evaluable. Absolute neutrophil count (ANC) < 1000 μL for 54 days in arm A versus 68 days in arm B ($P = 0.02$); platelets (PLT) count $<$ 25.000 μL: 57 days arm A versus 30 days in arm B ($P = 0.03$); days of hospitalisation 35 in arm A versus 16 in arm B ($P = 0.75$); platelets transfusion: 107 Vs 58 ($P = 0.02$); PRBCS 15 vs 5 ($P = 0.25$). No treatment related death occurred. At the present time, eight patients had responses and are alive. These data indicate that dose intensified CT may be delivered safely; GCSF alone shortens days of neutropenia, the combination of the 2 cytokines shortens the time of thrombocytopenia and decreases the number of platelets transfusions.

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EVALUATION OF THE EFFICACY OF G-CSF IN NEUTROPENIA INDUCED BY RT ALONE OR COMBINED WITH IMMUNOTHERAPY

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Extensive field irradiation of the pelvis induces neutropenia. The combination of RT with interferon results in a lower absolute neutrophil count. Thirty patients (pts) with stage III cancer of the uterine cervix were treated either with exclusive RT (group A, 10 pts) or with RT and 3.000.000 iu/d interferon plus isoretinoin 30 mg/d (group B, 20 pts). The immunotherapy duration was 2 months. The total RT dose in both groups was 54 Gy external beam RT and 20 Gy intracavitary Brachytherapy. The absolute neutrophil count of the beginning of the treatment did not exceed 4×10^8 I. G-CSF was administered only on days when the absolute neutrophil count was less then 2×10^9 I. G-CSF was not used prophylactically but upon indication. Neutropenia was corrected in all cases. Patients undergoing RT received at least 4 injections and the ones with the combined modality treatment 6–8 injections during the overall treatment time. The correction of the absolute neutrophil count allowed the continuation of treatment without interruptions that influence the local control. The efficacy of the G-CSF administration was immediately detectable. The neutrophil count rose to $5–6 \times 10^9$ I, on the following day, thus being promptly corrected. No adverse effects of G-CSF were observed. These results show the efficacy of G-CSF that can be used upon indication and not prophylactically.