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GRANULOCYTE COLONY STIMULATING FACTOR (G-CSF) ACTIVITY IN PREVENTION OF INFECTIONS IN NEUTROPENIC PATIENTS.

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In order to reduce duration of chemotherapy induced grade IV leucopenia, 28 cancer patients (pts) (14 males) underwent G-CSF treatment (5 mcg/kg). 37 neutropenic episodes were recorded, 6 pts displaying repeated events. Neoplastic disease were: 8 soft tissue sarcomas, 9 lung, 2 breast, 2 head & neck, 2 cervix, 1 gastric, 1 ovarian, 1 bladder, 1 testicular, 1 liver carcinoma. Median WBC nadir was 535/cmm. Mean time to bone marrow recovery after G-CSF treatment was 6.9 days. Infectious events were recorded during treatement in 16 pts (10 fungal, 2 St. Aureus, 3 unidentified agents). Death during treatment occurred in 4 pts: 2 for systemic infection, 1 for cancer progression, 1 for gastrointestinal bleeding. Median duration of antibiotic therapy was 9 days (range 4 - 23).
G-CSF may prevent fatal infectious episodes in G 4 neutropenic patients. Further investigation is required, in order to identify the optimal schedule of administration and the most active antibiotical therapy to be associated.

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RECOMBINANT HUMAN GRANULOCYTE COLONY STIMULATING FACTOR (R-MetHuG-CSF) IN PATIENTS WITH HODGKIN'S DISEASE AND NON-HODGKIN'S LYMPHOMA

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For both Hodgkin's disease and non-Hodgkin's lymphoma the outcome of chemotherapy has been shown to correlate closely with the dose intensity of treatment. However, dose intensification is limited most often by severe myelosuppression with the subsequent risk of fever and infections.

We performed a clinical trial in 17 patients with Hodgkin's disease or non-Hodgkin's lymphoma to evaluate whether r-metHuG-CSF could facilitate the safe and timely administration of an intensive chemotherapy regimen. Patients who developed neutropenia $\leq 0.5 \times 10^9$/L for more than two days and / or fever $\geq 38.2°C$ and / or signs of infection after a cycle of chemotherapy (CEBOPP/VIM protocol administered at intervals of 21 days), as well as patients in which chemotherapy had to be delayed due to an ANC $\leq 1.5 \times 10^9$/L on day 1, were eligible for treatment with r-metHuG-CSF. In the subsequent cycles r-metHuG-CSF was given subcutaneously at a dose of 5 µg/kg/d from day 11 to 20.

16 of 17 patients were evaluable, one patient had received only 1 day of r-metHuG-CSF treatment. 15 of the 16 evaluable patients experienced neutropenia with an ANC of less than 0.5×10^9/L during the chemotherapy course preceeding r-metHuG-CSF treatment, whereas only 5 patients had ANCs $\leq 0.5 \times 10^9$/L after the subsequent therapy with r-metHuG-CSF ($p<0.01$).Overall analysis showed that the duration of ANC nadirs $\leq 0.5 \times 10^9$/L was on average 3.27 days in 41 cycles without r-metHuG-CSF compared to 1.78 days in 52 cycles with r-metHuG-CSF treatment. The administration of chemotherapy had to be delayed only for 2.47 days (mean value) during cycles with r-metHuG-CSF. Side effects probably related to r-metHuG-CSF, were moderate muscle and joint pain in 3 patients and chills in one patient. In general, r-metHuG-CSF was well tolerated. Under this treatment regimen 11 patients reached complete remission, 4 patients reached partial remission and one patient had stable disease. One patient was treated adjuvantly after gastrectomy.

In conclusion, r-metHuG-CSF allowed the safe and timely administration of this intensive chemotherapy regimen and reduced myelosuppression for patients with Hodgkin's disease and non-Hodgkin's lymphoma.

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NEOADJUVANT CHEMOTHERAPY (EAP) WITH r-metHuG-CSF (FILGRASTIM) FOR PATIENTS WITH LOCALLY ADVANCED GASTRIC CANCER

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The poor prognosis in patients with locally advanced gastric cancer (LAGC) can only be significantly improved, if a complete resection (RO: UICC 1987) is performed. To increase the number of RO resections we performed a phase II trial using neo adjuvant chemotherapy with etoposide, adriamycin and cisplatinum (EAP) (Proc. ASCO 6:100, 1988).
Clinical staging included endoscopic ultrasound and laparoscopy. 31 patients were eligible, 30 patients (1 too early) (22 m, 8 f; median age 51.8 years; clinical stages (AJCC 1987), IIIA = 8, IIIB = 12, IV = 10) were evaluable for response, toxicity and survival after an average of 3 cycles CTx (1 - 4 cycles). In the last 14 patients Filgrastim (5µ/kg/die) was given from day 9 until day 21 or neutrophil recovery to normal levels in each cycle. Toxicity (WHO grade) included without or with Filgrastim leucocytopenia 3° and 4° (43.8% vs. 35.7%; 25% vs 7.1%), thrombocytopenia 3° and 4° (18.6% vs. 21.4%; 31.3% vs. 21.4%). In the Filgrastim treated group only 1 patient (7.1%) developed fever. Neither antibiotics nor hospitalisation due to febrile neutropenia were necessary in this group. Side effects due to Filgrastim were minimal. Moreover treatment duration was shortened with Filgrastim. Patients who received 3 cycles of EAP had an average reduction in chemotherapy treatment duration of 24 days compared to the non-Filgrastim group (110 vs 86 days from CTx-start until surgery), patients who received 4 cycles had an average reduction of 19 days vs the non-Filgrastim group (129 vs 110 days). Clinical response to EAP did not differ significantly.

Results after CTx and surgery: RO resections (24/30) (80%). Morbidity was not increased and no mortality was observed after surgery. After a follow-up of 24 months median (4 - 54 months) overall survival was 16.3 months with 23 months for RO resection.

Conclusion: Neoadjuvant CTx is feasible and very effective in patients with LAGC. If RO resection is achieved. Filgrastim completely abolished the occurence of life threatening infections due to neutropenia and allowed to increase the dose intensity.

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PREOPERATIVE CHEMOTHERAPY WITH R-metHuG-CSF SUPPORT IN PATIENTS WITH NON SMALL CELL LUNG CANCER - A PILOT STUDY

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In NSCLC 70% of patients are inoperable at the time of diagnosis due to the local extent of tumor spread. However, 30% of patients respond to chemotherapy (CT). Therefore we tested whether CT would induce sufficient tumor regression to allow for posttreatment surgery with curative intent.

The following chemotherapeutic regimens were used: cisplatinum/vindesine, ifosfamide/etoposide or cisplatinum/ ifosfamide/etoposide prior to surgery.The main dose limiting toxicity of these regimens is myelosuppression.
To avoid profound neutropenia and subsequent treatment delays, r-metHuG-CSF (Filgrastim) was used in 20 pts. as an adjunct to CT with cisplatinum/ ifosfamide/etoposide in an open-label, non-comparative phase II-trial. CT with G-CSF support was given at 3 weeks intervals in this group.
4 of the 20 patients included in this trial experienced an infectious episode during treatment. Neutropenia ≥ WHO grade III occurred in 11 patients and thrombocytopenia ≥ WHO grade III in 6 patients. In general, treatment with G-CSF was tolerated well and no G-CSF related adverse events were recorded.
18 of the 20 patients were evaluable for response to pre-operative CT, two patients had only received one CT cycle. Of the 18 evaluable patients,12 pts. achieved a partial response (PR), and one patient had a minor response (MR). In comparison of 14 evaluable patients treated previously at the same institution with the same CT at 4 weeks intervals without G-CSF support 1 pt. reached CR, 2 had PR and 2 pts. had minor response (MR). Of 25 pts. who had received either DDP/vindesine or ifosfamide/etoposide at 4 weeks intervals, 5 reached PR and 7 MR.

In conclusion G-CSF was well tolerated and allowed for dose intensification by shortening the CT intervals. These data may indicate an improved response rate in this group compared to patients receiving CT at longer intervals without G-CSF support.

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TREATMENT OF LEUCOPENIA USING RECOMBINANT GRANULOCYTE-COLONY STIMULATING FACTOR IN IRRADIATED TUMOR PATIENTS

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In patients receiving an extensive radiotherapy neutropenia is often the reason of treatment discontinuation. In case of advanced carcinoma, there is an increased risk of infection. The purpose of our study was to find out whether recombinant granulocyte-colony stimulating factor (rG-CSF) can reduce the number of days without radiotherapy due to leucopenia and diminish the risk of infection.
22 irradiated patients with diagnosed leucopenia (Hodgkin's disease-10, NHL-7, ALL-1, CLL-1, breast carcinoma-3) were treated with the growth factor. 300µg of rG-CSF were given subcutaneously for 1-5 days. In all patients a significant increase in leucocyte counts was observed. After discontinuation of rG-CSF treatment, leucocyte counts decreased rapidly and reached normal or subnormal levels. The duration of treatment interruptions was reduced. No severe infections were observed. Our study demonstrates, that rG-CSF is an efficiant factor in the treatment of leucopenia under radiotherapy. The dose necessary to control the decrease of granulocyte counts is lower compared to patients receiving chemotherapy and indicates that dosage recommendation for radiotherapy patients should be defined.

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HIGH-DOSE CHEMOTHERAPY AND GM-CSF AFTER STANDARD CHEMOTHERAPY FOLLOWED BY AUTOLOGOUS TRANSPLANTATION OF PERIPHERAL BLOOD STEM CELLS.

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An ongoing study is being carried out to:1)evaluate the feasibility of associating high-dose cyclophosphamide (HD CTX) and carboplatinum (HD CBDCA) with GM-CSF after conventional chemotherapy (CT); 2) ascertain whether this treatment yields sufficient peripheral blood stem cells (PBSC) for subsequent autologous transplantation (APBSCT). 7g/m² CTX is given in the 1st cycle, 800 mg/m² CBDCA in the 2nd cycle and, should insufficient PBSC be collected for APBSCT, a further cycle of CTX is given at the same dose as in the 1st cycle.GM-CSF (5µg/Kg/day) is given for 14-18 days after completion of each CT cycle. Seven patients (3 NH, 2HD, 2NHL), a mean age of 46 yrs (35-55) have been entered in the study. Six have completed CT: 1 received 2 and 3 patients 3 cycles, the other is still on CT. 53.4 and 64 GM-CFUx10/Kg were collected from 2 of the 3 who received 2 cycles and 4.5 from the 3rd.The number of GM-CFUx10/Kg for the 3 who received 3 cycles ranged from 17.3 to 37.7 GM-CFUx10/Kg, but in 2 patients leukapheresis could only be carried out after 2 of the 3 CT cycles. Two NH patients have already been infused, the 1st with 53 GM-CFUx10/Kg,the 2nd with 23 after being conditioned with busulfan 4 mg/Kg/day p.o from days -7 to -4 and melphalan 140 mg/m²iv on day-3.GM-CSF (10µg/Kg/day) was administered from the day after the reinfusion in both case.One achieved full hematological recovery on the 7th day, the other on the 10th day. This preliminary study indicates that HDC is feasible after conventional CT and that 2-3 cycles are sufficient to obtain adequate PBSC for APBSCT. Moreover if the data are confirmed in the future,aplasia is shorter post-APBSCT+GM-CSF that in other reported studies