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Combined therapy of amifostine and gemcitabine in high-risk myelodysplastic syndromes

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Patients with myelodysplastic syndromes (MDS) have two major problems: cytopenia and transformation in acute myeloid leukemia. In this context, amifostine has been shown to promote in vitro formation of hematopoietic progenitors and induce hematologic improvement.

Patients with refractory anemia with excess of blasts and some other patients with either poor risk factors for survival or increased risk of transformation in a myeloid leukemia are in need of cytotoxic therapy. Gemcitabine is a novel deoxycytidine analogue with similarities, but also some differences to cytarabine, e.g. the so-called "masked chain termination" of the DNA. Long-term infusions of gemcitabine result in higher intracellular concentrations of the active metabolite as compared to the standard application over 30 min. We, therefore, initiated a phase I study in which we combine weekly infusions of gemcitabine over 6 hours with amifostine. A fixed dose of 200 mg/m^2 amifostine is given three times a week. The starting dose of gemcitabine is 75 mg/m^2 and will be escalated in 75 mg/m^2 steps.

Progenitor cell cultures with and without amifostine and gemcitabine are performed to examine the correlation of in vitro and in vivo effects. Different scoring systems, histopathologic parameters, cytogenetic abnormalities, and immunophenotype will be presented to determine subgroups of patients with different probabilities of response.

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Antiblastic activity bifunctional platinum-6-mercaptopurin and monoclonal antibody conjugate

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Purpose: The purpose of the investigation is increasing antiblastic activity and reducing toxicity of the cytostatic drugs. We have worked out a new technology of obtaining immunoconjugates of promising platinum and 6-mercaptopurin complex (Pt-6-mp). As a carrier, in the given case, we used monoclonal antibodies, specific to the K-562 human leukemic cells antigens.

Methods: Platinum content in conjugate was established by means of the neutron assay and chemical methods. Testing has been carried out in vitro and in vivo.

Results: The immunoconjugate we developed have shown a higher dose-dependent cytotoxic activity on leukemic target cells than that of the initial Pt-6-mp complex and antibodies. A study of hematotoxicity (BALB/c mice model) of Pt-6-mp immunoconjugate revealed that the use of the conjugate did not result in developing leucopenia (BALB/c mice model) which testifies to their low hematoxic effect.

The data obtained can be of certain interest in selectivity schemes of cytostatic therapy and leukemic bone marrow cells elimination

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Analysis of pulmonary infections during high-dose chemotherapy (HDC) and peripheral blood stem cell autologous transplantation (PBSCT)

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Purpose: Pulmonary infectious (PI) are frequent and serious events in the course of bone marrow transplantation. We analyze PI associated to PBSCT which is a new technique of hematopoietic support.

Methods: One hundred and thirty two pts with lymphomas (6 pts) or solid tumors (126 pts) were treated with HDC and PBSC. A minimum of 2 × 10^6 CD34+ cells/Kg was infused with G-CSF 5 ugr/Kg/d in 122 pts. All pts received an antimicrobial prophylaxis with Ciprofloxacin 500 mg p.o./12 h, Acyclovir 200 mg p.o./6 h, Itraconazole 200 mg/12 h and stayed in single rooms with HEPA. Imipenem 500 mg/6 h was started when temperature was >38°. If fever persisted Vancomycin 1 g/12 h and Amikacin 7.5 mg/Kg/12 h were added after 2–3 and 5 days respectively. Amphotericin 1 mg/Kg/d was started after 7–8 days of fever. When a pneumonia was diagnosed, pts received Imipenem, Vancomicin and Amikacin. Bronchoalveolar lavage (BAL) was performed after 48 h if there was no response and addition of new antibiotic was evaluated: Erythromycin ± Cotrimoxazole ± Amphotericin.

Results: Median days to 0.5 × 10^9 neutrophil/L was 9 (5–30) and to 20 × 10^9 platelet/L 11 (7–42). There were 2 toxic deaths (1.5%). Eleven pts (8%) developed a PI: 9 pneumonias and 2 aspergillosis. Two had a lymphoma and 9 a solid tumor. Two pts had positive blood cultures, one for Pseudomonas alcaligenes and one for Staphylococcus epidermidis, both catheter-associated. BAL was performed in 6 pts, 5 were negative and one positive for Aspergillus. Erythromycin was added to 5 pts, Cotrimoxazole to 2 pts and Amphotericin to 3 pts. The two aspergillosis were resolved. Only one pt required mechanical ventilation, no germens were isolated, and died in the ICU.

Conclusions: 1. Pulmonary infections persist as a serious event in pts submitted to HDC with PBSCT. 2. Overall and pulmonary infection mortality in the PBSCT setting is lower than previously reported with autologous bone marrow transplantation, probably due to a shorter period of neutropenia and a more rapid immunological recovery. 3. An early agressive empirical antibiotherapy is mandatory.

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Lymphocyte abnormalities during post-chemotherapy myelosuppression and bone marrow regeneration in patients with solid tumors

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Purpose: The comparative study of quantitative and qualitative alterations of lymphocyte subsets during post-chemotherapy myelosuppression and bone marrow regeneration induced by rhG-CSF

Methods: Fifty three cancer patients with more than grade 2 post-chemotherapy neutropenia and 10 normal blood donors were studied. Whole peripheral blood was obtained during the nadir of neutrophils, before the administration of rhG-CSF and after bone marrow regeneration. Lymphocyte subsets (T-, B-, and NK-cells) were evaluated by indirect immunofluorescence; cell proliferation, was studied upon PHA-P or anti-CD3 moAb stimulation of whole blood cultures.

Results: The absolute lymphocyte number (ALN) of cancer patients was significantly lower during post-chemotherapy myelosuppression than in normal blood donors (m ± SE: 819 ± 74 cells/dl vs 1601 ± 64 cells/dl; p = 0.001). Lymphopenia concerned the CD3$^+$ (667 ± 61 cells/dl; p = 0.001), CD4$^+$ (375 ± 38 cells/dl; p = 0.001); and CD20$^+$ (172 ± 24 cells/dl; p = 0.001) but not the CD8$^+$, or CD56$^+$ (NK) cells. The ALN was significantly higher during bone marrow regeneration (175 ± 156 cells/dl; p = 0.001) than during myelosuppression (1042 ± 101 cells/dl). The increase of lymphocytes concerned all studied lymphocyte subsets, as well as cells bearing activation-associated molecules (HLA-DR and CD25). The increase of CD25+ cells concerned the CD4$^+$ (p = 0.001) but not the CD8$^+$ cell subset. Eleven out of 53 (21%) patients displayed less than 400 CD4$^+$ cells/dl during bone marrow regeneration. Spontaneous cell proliferation and anti-CD3– but not PHA-P-induced cell proliferation were significantly higher during bone marrow regeneration than during post-chemotherapy myelosuppression. Moreover, during bone marrow regeneration, PHA-P and anti-CD3 moAb failed to enhance proliferation of peripheral blood lymphocytes in 15 (60%) of 25 and 11 (44%) of 25 patients respectively.

Conclusions: Chemotherapy-induced myelosuppression is associated with a significant lymphopenia but, in general, an active lymphopoiesis takes place during bone marrow regeneration. However, a substantial number of patients present important quantitative and qualitative abnormalities of T cells during the regeneration of bone marrow suggesting an impaired cell-mediated immunity in these patients.