Symposia

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STEM CELLS AND GROWTH FACTORS: WHAT REGULATES WHAT?

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CSFs are a class of growth factors in that they are necessary for the survival, proliferation and maturation of blood cells without being nutrients. However, their exact role in the control of very early stages or baseline hemopoiesis remain unclear. *In vivo*, peripheral blood cell numbers are often inversely related to the concentration in serum of specific growth factors: circulating monocytes and M-CSF, granulocytes and G-CSF, platelets and thrombopoietin. *In vitro*, the considerable increase in the numbers of lineage-committed CD34+ cells following growth factor treatment usually lead, by promoting differentiation, to a decrease or disappearance of the most primitive lineage uncommitted CD34+ population in which the true self-renewing stem cell likely resides. Until more is known about these most primitive cells, it may prove easier to control *ex vivo* the differentiation of maturing blood cells by appropriate combinations of cytokines (e.g. to generate specific subsets of immunocompetent cells with anti-tumor or anti-viral activity) than to truly expand hemopoietic stem cells. However, the *ex vivo* expansion of progenitor cells to enhance recovery is feasible.

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EX VIVO MANIPULATION AND CLINICAL USE OF PERIPHERAL BLOOD PROGENITOR CELLS IN CANCER PATIENTS

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Peripheral blood progenitor cells (PBPCs) are being used increasingly for autologous stem cell transplantation after high-dose chemotherapy in both solid tumors and hematological malignancies.

To minimize tumor cell contamination of PBPC collections, we have reduced the total volume of blood processed from the patients, followed by expansion of PBPCs *ex vivo*. We have shown that a combination of SCF, IL-1β, IL-3, IL-6 and Epo mediates the *ex vivo* expansion of clonogenic progenitor cells of various hematopoietic lineages and, moreover, that primitive hematopoletic stem cells, as quantitated by long-term culture initiating cells (LTC-IC), could be preserved. These preclinical studies suggested that *ex vivo* expanded peripheral blood $CD34^+$cells might be able to mediate both, short-term as well as long-term hematopoietic reconstitution following high dose chemotherapy. In a phase I/II trial, we investigated the transplantation potential of *ex vivo* expanded $CD34^+$ PBPCs in solid tumor patients undergoing high-dose chemotherapy. Ten patients were transplanted with *ex vivo* expanded PBPCs, starting from a fixed number of 1.1×10^7; peripheral blood $CD34^+$ cells, a cell number which corresponds to less than 1/10th of our standard 2-hour leukapheresis preparation. The study showed that this approach is feasible and that *ex vivo* expanded cells mediate rapid and sustained hematopoietic recovery when transplanted after high-dose VIC-chemotherapy. The reconstitution pattern was identical to that of historical control patients who had been treated with unseparated PBPCs or positively selected peripheral blood $CD34^+$cells. Thus, starting from a small number of peripheral blood $CD34^+$cells, *ex vivo* expanded hematopoietic progenitor cells might offer new prospects for cellular therapy, including a reduced risk for tumor cell contamination, the circumvention of leukapheresis, the potential for *ex vivo* manipulation, as well as the potential for repetitive cycles of high-dose therapy.

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PERIPHERAL BLOOD PROGENITOR CELLS (PBPC) AND TREATMENT OF NON-HODGKIN'S LYMPHOMA

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Autologous stem cell transplantation (ASCT) has been integrated routinely in the treatment of relapsing or histologically aggressive poor prognosis NHL. Comparison of bone marrow (BMT) (72 pts) with PBPC (78 pts) transplantation showed that PBPC was a safer procedure. Hematopoietic recovery was accelerated for neutrophils and platelets as compared with BMT and was associated with lower toxicity. The engraftment persisted in long-term studies and any difference in failure free survival was reported. Recently the therapeutic efficacy of ASCT with PBPC was evaluated in 60 relapsing follicular lymphoma patients. At 2 years overall survival and failure free survival were 86% and 53% respectively. Survival was not affected by the presence or not of residual bone marrow involvement at the time of collection. Purification of blood product after CD34+ selection is presently under study in order to increase the quality of blood product and will be tested to try to improve clinical results.

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T-CELL DEPLETED HAPLOIDENTICAL "THREE LOCI" MISMATCHED MARROW TRANSPLANTS BY ADDITION OF T-CELL DEPLETED PERIPHERAL BLOOD PROGENITOR CELLS

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We have reported the successful engraftment of T-cell depleted "three loci" HLA-mismatched transplants in a preliminary series of 17 end-stage leukemia patients (Aversa *et al.*, *Blood* 1994, **84**, 3948;). Total of 35 patients (mean age 22 years, range 2–51) with high-risk leukemia (12 AML, 18 ALL and 5 CML) have been transplanted. Fourteen were in hematological remission at the time of transplant and 21 in chemoresistant relapse. All donors were HLA-haploidentical "three loci" incompatible family members (13 siblings, 21 parents and 1 cousin). Five patients rejected the graft, 3 died from aplasia but 2 achieved a stable engraftment after a second transplant from a different mismatched donor. A neutrophil count greater than 1.0×10^9/L was reached at a mean of 11 days and platelet count $>25 \times 10^9$/L at a mean of 17 days. Acute GvHD > grade II was observed in 4 of the 21 advanced leukemia (Group I) patients and in 1 of the 14 in remission (Group II) at the transplant. Among the Group I, 4 relapses occurred, 14 patients died from transplant related toxicity and 3 survive event-free at a follow-up of 12, 23, and 25 months post-transplant. In the Group II, one patient relapsed, three died from toxicity and 10 survive event-free ad a mean follow-up of 9 months (range 4–13). This approach should be applied to selected high-risk patients who do not have HLA-matched donors. Outcome depends on the stage of disease at the time of transplant, with very encouraging results achieved at hematological remission.

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MULTIPLE COURSES OF HIGH-DOSE ALKYLATING THERAPY WITH AUTOLOGOUS STEM CELL SUPPORT

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Since the introduction of autologous blood progenitor cell transplantation, (APCT) bone marrow suppression is no longer dose-limiting after high-dose therapy. We have developed a high-dose chemotherapy regimen 'CTC', that includes cyclophosphamide (6 g/m^2), thiotepa (480 mg/m^2) and carboplatin (1600 mg/m^2) administered over four days. This regimen has been shown to be well-tolerated in over 80 (first) courses and multiple courses could be feasible.

28 patients received 2 courses of CTC, CTC-2 beginning on day 28 after the first APCT. One patient died of sepsis, one developed reversible veno-occlusive disease (VOD). Eleven patients received 3 subsequent courses of CTC. There were three toxic deaths: 1 × sepsis, 1 × VOD, 1 × hemolytic uremic syndrome (HUS). Two other patients developed reversible VOD, one had reversible HUS. While two closely spaced CTC courses are feasible, three subsequent courses are associated with frequent unacceptable organ toxicity. Preliminary data of a phase I/II study in advanced breast cancer suggest that three tightly spaced 'tiny CTC' courses—containing 2/3 of the doses of each of the agents in a standard

CTC course—may be well-tolerated and are not associated with excess organ toxicity.

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IMAGING OF PROSTATE CANCER

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For the diagnosis of prostate cancer, transrectal ultrasonography (TRUS) is the only appropriate imaging tool. Its sensitivity can be further increased by systematically applying color-Doppler imaging.

TRUS is also a significant aid for biopsy guidance, either for focal lesions, to direct biopsies to suggestive and potentially involved areas, or for any set of systematic biopsies.

Magnetic Resonance (MR) imaging is the most useful tool for evaluation of local extension, especially to the seminal vesicles. As TRUS, MRI though has its limitations, particularly in the evaluation of microscopic disease.

It is presumed that patients at increased risk of lymph node metastases are most likely to benefit from CT or MRI and subsequent fine needle aspiration cytology when lymphadenopathy is found.

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SCREENING FOR PROSTATE CANCER

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Prostate cancer is the second most frequent malignant disease and the second most frequent cause of cancer death in men. Prostate cancer can be detected early by means of rectal examination (DRE), Protate Specific Antigen (PSA) and Transrectal Ultrasonography (TRUS). Obviously, advanced prostate cancer passes through a contined stage. Can it, however, be effectively identified and treated to decrease prostate cancer mortality and to improve overall life expectancy and quality of life?

A considerable number of case finding studies have been carried out and published. These show stage reduction at the time of diagnosis with respect to clinical routine. Tumours diagnosed in this way can more frequently be completely excised. Does this all translate into advantages which make early detection clinically worthwhile and acceptable as a public health policy? These questions are subject to the European Randomized Study of Screening for Prostate Cancer (ERSPC). Aspects of the natural history, the effectiveness of early detection tests, the effectiveness of treatment, the results of pilot studies, ethical problems of screening and issues of quality of life will be discussed.

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DEFERRED TREATMENT FOR EARLY STAGE PROSTATE CANCER

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The 1992 TNM classification introduced a new type of prostate cancer, diagnosed by needle biopsy because of a raised serum PSA, called T1c. If current North American fashion crosses the Atlantic thousands of unsuspecting European men will discover they have this disease and will seek treatment. Should immediate total prostatectomy, or radiotherapy, be recommended? Are T1c cancers "clinically significant?" Is "watchful waiting" appropriate? Do they behave as T1a, T1b or even T2 tumours?

Watchful waiting means regular review. Some men find this process very reassuring but others experience increasing anxiety and difficulty living with an untreated cancer. Deferred treatment implies treatment for progression. Should we wait for symptoms which for most will be painful metastases and palliative treatment only? Should treatment be triggered by increased in size of the primary tumour—will prostatectomy be too late? Should a rising PSA be treated? If so, at what level?

In many ways watchful waiting is more difficult for the physician than early "definitive" treatment but all forms of treatment are associated with significant morbidity. For the patient quality of life as well as longevity is of paramount importance.

The logical solution is a randomised trial. The Swedish study of surgery and watchful waiting for some forms of early prostate cancer has recruited over 400 patients. However, experience in the U.K. and North America suggests that treatment choice based on randomisation is not accepted by many of the patients. When "fully informed", many men have difficulty accepting such different treatments by random allocation. How should we proceed? Should patients be less informed? Should trials be based on post-randomisation consent? Should PSA for early detection be made available only to those men who will accept treatment in a randomised trial? Is it possible to devise statistical methods that overcome the biases introduced by allowing patients to choose? There are no easy solutions but thoughtful, informed and open debate is urgently needed.

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THE ROLE OF EXTERNAL IRRADIATION IN EARLY PROSTATE CANCER

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In Europe, the incidence of prostatic carcinoma is increasing, certainly due to both a better declaration of cause of death to cancer registries, and an increased practice of individual screening in men by serum determination of PSA. Consequently the clinical diagnosis is more and more frequently done at a loco-regional stage such as T1T2. When we look at the long term results of external irradiation, survival and progression free survival are progressively decreasing and the higher the clinical stage, the poorer the prognosis. From a radio-therapeutic standpoint many issues remain unanswered, which could have an impact on survival, concerning: the assessment of lymph node status by laparoscopic procedures, the opportunity of hormonal treatment (neo-adjuvant or adjuvant), the indications of post-operative radiotherapy after radical prostatectomy, elevated PSA after definitive radiotherapy, a better understanding of the tumoral phenotype. 3D conformal radiotherapy, inverse dosimetry and electronic portal imaging device represent a major breakthrough which enable the radiation oncologist to adapt the isodose as closely as possible to a customized target volume, to improve patient set-up accuracy, and why not, in the near future to improve local control and survival among negative pelvic lymph node patients, as well.

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RADICAL PROSTATECTOMY

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Radical prostatectomy has become a standard operation attempting cure for localized prostate cancer. Advances in diagnosis enable the identification of the disease at an early stage when more patients are curable and refined techniques for staging have improved the selection of surgical candidates. Radical prostatectomy should be reserved for those patients who can be cured and who will live long enough to benefit from it. It is possible to cure many patients with organ confined cancer and some patients with specimen confined tumors. With the ability of wide tumor excision, clinical local recurrence rates are low although biochemical recurrence is much more frequent, and most patients who fail do so from distant metastases. All efforts should be undertaken to diagnose this increasing and life threatening disease in the earliest stages.

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NOVEL RADIATION MODIFIERS

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The clinical approaches toward radiosensitization have utilized a number of different concepts including hypoxic cell sensitization, halopyrimidine-based radiosensitization and the use of combined modality therapy with chemotherapy plus irradiation. There are currently a new set of agents undergoing clinical trials called radiation enhancers or hypoxic-cytotoxic agents. These agents are designed to kill poorly perfused cells, which might limit the success of both radiation therapy and chemotherapy. Unlike the hypoxic sensitizers or oxygen modifiers, these agents can produce sensitization when given either before or *after* radiation.

Based on the emerging knowledge of the cellular and molecular responses to ionizing radiation, novel agents are being conceptualized that may alter both tumor and normal tissue response.

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