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QUANTITATIVE POLYMERASE CHAIN REACTION FOR EARLY DETECTION OF IMPENDING RELAPSE AND FOR THE MONITORING OF REMISSION IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA

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In patients with chronic myeloid leukemia (CML) after chemotherapy or bone marrow transplantation (BMT), the early identification of individuals who have a high risk of relapse is a necessary prerequisite for determining the possible need of additional therapy. Application of the highly sensitive polymerase chain reaction (PCR) to the detection of residual leukemic cells carrying the characteristic BCR/ABL rearrangement was shown to be of limited prognostic value, because a number of patients display residual rearranged cells for many years without progressing to relapse. We have therefore developed a quantitative PCR protocol which facilitates the monitoring of the proliferative activity of the residual neoplastic cells and we showed in patients after BMT that the detection of an expanding neoplastic clone by quantitative PCR, which we termed "PCR relapse", may precede clinical relapse by several months. The early identification of an incipient relapse provides a rationale for the timely initiation of treatment directed at the eradication of a small residual neoplastic clone. Moreover, our preliminary results obtained by quantitative PCR-analyses in CML patients under therapy with IFN suggest that the efficacy of treatment can be assessed and monitored at the sensitivity level of PCR, thus providing a potential basis for appropriate dosage adjustments. In addition to the early detection of impending relapse, quantitative PCR analyses in CML patients may be useful in the monitoring of the quality of remission.

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HAEMATOLOGICAL, CYTOGENETIC AND MOLECULAR RESPONSE IN CML PATIENTS TREATED WITH HIGH-DOSE CHEMOTHERAPY AT DIAGNOSIS, IN THE ACCELERATED PHASE OR BLASTIC CRISIS.

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Eleven CML patients were treated with a high-dose chemotherapy regimen of 6-8 mg/m² Idarubicin (I) given for 3 or 5 consecutive days, 400-1000 mg/m² Cytosine-Arabinoside (Ara-C) given for 3 or 5 consecutive days and 100-150 mg/m² Etoposide (VP-16) from days 1-3.One to three cycles were planned.One patient was treated at diagnosis, 5 in late chronic phase, 3 in accelerated phase and 2 in blastic crisis.The highest dose of all 3 agents was administered during the 2nd and 3rd cycles.Two patients have received one, 4 two and 5 three cycles.Haematological response was complete in the patient treated at diagnosis, in 3/8 chronic-accelerated phase and in 1/2 blastic crisis patients; it was partial in 5/8 chronic-accelerated phase patients.Cytogenetic response is still being evaluated in the patient treated at diagnosis.Two/8 chronic-accelerated phase patients achieved complete sustained cytogenetic response after the 2nd cycle, 3 minor transitory reponse (65%, 38%, 12% Ph' negative metaphases) after the 1st cycle. A patient had 64% Ph' negative peripheral blood metephases after the 1st cycle. One patient in blastic crisis achieved partial (61% negativity) cytogenetic response in the bonemarrow while peripheral blood cells were 100% negative.PCR revealed bcr/abl transcript in 100% Ph' negative peripheral blood cells.The present data indicate that Ph' negative cells are able to repopulate the bone marrow after high-dose chemotherapy even during late chronic phase, accelerated phase and blastic crisis .The molecular data show that the chemotherapy schedule needs to be further intensified in order to obtain greater suppression of the leukaemic clone.

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LONG-TERM CYTOGENETIC RESPONSE TO IFN-α, IFN-α FOLLOWED BY THE ASSOCIATION WITH LOW-DOSE ARA-C OR HIGH-DOSE CHEMOTHERAPY IN CML PATIENTS.

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Forty-nine consecutive chronic phase CML patients (34 M, 15 F), mean age 48 yrs (range 21-72) have been treated with rIFN-α since 1986 at our institute; 26 newly diagnosed, 6 early phase (within 12 months of diagnosis) and 17 late (more than 1 yr on standard chemotherapy). Cytogenetic response was documented in 21 of the 46 patients who were Ph'+. Twenty were followed up for more than 1 yr (median 45, range 12-76 months). Therapy was interrupted in the other patient for allogeneic BMT. Fifteen started therapy at diagnosis or in the early phase and 6 in the late phase. Five obtained complete, 10 partial (35-95 % negativity) and 6 minor (< 35 % negativity) cytogenetic response. Five of the complete responses were in newly diagnosed or early phase patients and one in a late phase patient. Response occurred within 12 months in 18 and within 18 months in 3 patients. Median response duration was 18 months (range 6-40). Eight / 49 patients who were refractory to IFN-α (7 chronic phase, 1 blastic crisis) received high-dose chemotherapy (5), IFN-α + low-dose ARA-C (2) or natural IFN-α (1). Two achieved complete and 2 minor cytogenetic response (3 chronic phase, 1 blastic crisis). The present data indicate that residual normal haematopoiesis persists in CML patients and that IFN-α favours its expansion. The 4 patients who obtained a second cytogenetic response are evidence that this may occur more than once during the course of the disease when different, progressively more intensive therapeutic regimens are employed.

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VAD-PECC REGIMEN IN THE TREATMENT OF ADVANCED STAGE MULTIPLE MYELOMA.

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Eighty patients have been enrolled in a prospective study on the efficacy of a sequential schedule derived from the VAD regimen : VAD = vincristine 0.4 mg/d d 1-4 continuous IV infusion (CIV), adriamycin 9 mg/m2/d d1-4 CIV, dexamethazone 40 mg/d d1-4 ; PECC = aldisine 3 mg/m2 d 35, BCNU 30 mg/m2 d1, cyclophosphamide 1g/m2 d35, prednisolone 50 mg/m2 d35-39. After 4 months of stable disease, oral monthly therapy was given (prednisolone 0.5 mg/kg weeks 1 and 3, melphalan 0.05 mg/kg week 2, cyclophosphamide 2.5 mg/kg week 4).
They were 45 men, 35 women aged from 42 to 80 yrs (median = 63), with de novo stage III (Durie Salmon) multiple myeloma (MM) (group A : n=44, 24 men, 20 women, aged from 44 to 80 (median =64)), or with stage I or II MM progressing after an oral melphalan based chemotherapy (group B : n = 36, 21 men, 15 women aged from 42 to 77 (median =62), time from diagnosis 4 to 92 months (median 30)). Immunoglobulin type was IgG in 41 cases, IgA in 25 cases, IgD in 3 case, light chain in 10 cases. One patient had non-secreting MM. Sixteen patients had renal impairment (group A : 10 ; group B : 6). Karnofsky index at inclusion ranged from 20 to 100 : A : 20 to 100 (median 80) B: 40 to 100 (median 70). The median number of cycles administered in group A was 6 (range 1-15), and was 5 in group B (range 1-9). In group A, we observed 8 grade 3-4 haematological toxicities, 7 grade 3-4 infectious toxicities, 2 grade 2, 1 grade 3 cardiac function toxicities. In group B, we observed 8 grade 3-4 haematological toxicities, 8 grade 3-4 infectious toxicities, 1 grade 2, 2 grade 3 cardiac dysfunctions.
The median duration of follow up of all surviving patients is 44 months. Overall median survival from diagnosis for all patients is 53 months. In group A, overall median survival is 53 months. In group B, overall median survival is 18 months after the beginning of VAD-PECC, and 52 months after diagnosis.
We conclude that VAD-PECC is able to provide long term survivals for patients with advanced MM. The survival of patients with de novo stage III is similar to that of patients with an initial low tumour burden progressing after an initial oral therapy.

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THE POSSIBLE ADDISIONAL REASON OF IMMUNODEFICIENCY IN SOME FORMS OF HEMOBLASTOSIS

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The immunodeficiency(ID)always occurs in the forms of hemoblastosis when tumour substrate is represented by immunocompetent cells(ICC),e.g.in non Hodgkin's lymphomas and myelomas.The main reason of the ID development in these diseases certainly is the decrease of normal ICC count by their malignization,but one should as well take into consideration other processes promoting ID.Electronmicroscopic studies of the blood cells of 22 patients with lymphomas and 10 with myelomas constantly showed a certain count of polykaryocytes:multinuclear cellular structures formed by fusion of ICC.In particular the count of polykaryocyt was 3-8% of the ICC total count.As polykaryocytes are functionally unable and cannot proliferate we assume that their formation in these diseases may be considered as a process of ICC ellimination and accordingly as a possible additional reason for the development of ID.

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BUSULFAN-MELPHALAN CONDITIONING PRIOR TO BONE MARROW TRANSPLANTATION FOR POOR-RISK LEUKEMIA. Mehta J, Powles RL, Treleaven J, Milan S. Leukaemia Unit, Royal Marsden Hospital, Sutton, Surrey SM2 5PT, UK.

13 patients (7 male, 6 female) aged 17-49 years (median 32) underwent syngeneic (1), matched sibling (7) or matched unrelated donor (1) BMT, or autologous BMT (3) or peripheral blood stem cell transplant (1) for advanced poor-risk leukemia. The diagnoses were: Secondary AML in first CR (1), biphenotypic leukemia with severe marrow fibrosis (1), CML in blast crisis (2), relapsed CML after previous syngeneic BMT (1), ALL in first relapse (1), ALL in second relapse (4; 1 relapse after previous ABMT), ALL in third CR, AML in second CR (1), and AML in third relapse (1). The conditioning chemotherapy was busulfan (16 mg/kg) and melphalan (110 mg/m^2). 3 (23%) of the patients are alive disease-free 8-10 months (median 9) after BMT. The causes of death were: relapse (3), acute GVHD (2), pneumonia (2), pneumococcal septicemia (1), renal failure (1), and sepsis (1). We conclude that busulfan-melphalan may be an effective preparative regimen for BMT and needs to be studied in standard risk patients. It may not be immunosuppressive enough to allow consistent engraftment of allogeneic marrow.