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THE IMMUNOHISTOCHEMICAL DETECTION OF CSF-1 (COLONY STIMULATING FACTOR-1) IN PRIMARY BREAST ADENOCARCINOMAS CORRELATES WITH MARKED INFLAMMATORY CELL INFILTRATES.

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The prevalence and prognostic value of specific tumour infiltrating lymphocytes (TIL's) and monocytes (TIM's) in 196 human breast tumours was assessed by immunohistochemical techniques. Markedly high numbers of CD45RO-positive T and L26-positive B cell infiltrates were present in 13% and 17% respectively of this random population treated with first line surgery, whereas minor T and B cell infiltrates were present in additional 22% and 25% respectively. CSF-1 receptor positive monocytes were detected in 48% of all tumours and monocytes (CD68+) were present in 90% of tumours and represented more than 20% of the total infiltrate in 51% of all tumours. CSF-1, a known monocyte chemoattractant and growth stimulant was expressed significantly (>10% cells staining positively) in 73% and the CSF-1 receptor in 58% of these tumours. Tumours with high percentage of CSF-1 expressing cells, also had marked monocyte infiltrates ($p = 0.036$). In turn, tumours presenting large fractions (>20%) of CD68 positive monocytes also showed CSF-1 receptor positive monocytes ($p < 0.0001$) as well as a marked non-specific immune cell infiltrate (ICI) ($p = 0.003$). Furthermore, the cytoplasmic localisation of CSF-1 staining in tumour cells was correlated with the presence of marked CD45RO-positive T cell ($p = 0.007$) and L26-positive B cell ($p = 0.041$) infiltrates. An unexpected result was the association between nuclear staining of CSF-1 in tumour cells with the occurences of metastases ($p = 0.004$) and with poor survival ($p = 0.003$). Nuclear retention of CSF-1 might be a reflection of CSF-1 receptor turnover and function, similarly to the sequestration and retention of radiolabelled estrogens in estrogen receptor positive target organs.

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PHASE I TRIAL OF PIXY321 IN COMBINATION WITH CYCLOPHOSPHAMIDE (Cy) AND CARBOPLATIN (Carb) IN WOMEN WITH OVARIAN CANCER (OC).

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PIXY321 is a recombinant fusion protein of GM-CSF/IL3. We conducted a Phase I trial of PIXY321 in combination with Cy 600mg/m^2 + Carb 400mg/m^2 iv q4 wk x6 in women with OC. After the 1st cycle pts received no cytokine. In subsequent cycles chemo Rx was followed by PIXY321 sq on d 3-17 given once or twice daily to groups of pts in doses from 50-1000ug/m^2. 34 pts are entered. Toxicities include: malaise, headache, nausea, vomiting, fever, chills, chest tightness (1 pt), and swelling/induration at injection sites.

Dose	Median Nadir Platelets			Median Nadir ANC		
PIXY321	Cycle 1(n)	2(n)	3(n)	1(n)	2(n)	3(n)
50 qd	36(3)	55(3)	35(2)	492(3)	308(3)	334(2)
125 qd	187(2)	137(2)	80(2)	780(2)	712(2)	521(2)
250 qd	204(3)	95(2)	90(3)	1184(3)	186(3)	300(3)
500 qd	64(6)	71(6)	36(4)	192(6)	586(6)	392(4)
750 qd	70(6)	111(6)	89(5)	312(6)	478(6)	340(5)
375 bid	72(6)	101(6)	76(3)	725(6)	557(6)	650(3)

PIXY321 shows marrow stimulation for both ANC and plts suggesting both parts of the fusion protein are active.

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MEGAKARYOCYTE GROWTH FACTORS IN SERA OF THROMBOCYTOPENIC PATIENTS UNDERGOING CHEMOTHERAPY, RADIOTHERAPY OR ALLOGENEIC BONE MARROW TRANSPLANTATION

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Thrombocytopenic sera contain megakaryocyte (MK) colony stimulating activity (CSA) which supports growth of MK colonies (CFU-MK), but remains unidentified. In search of MK growth factors, sera from thrombocytopenic cancer patients were screened for MK-CSA. Sera from thrombocytopenic ovarian cancer patients treated with carboplatin induced only a few CFU-MK, 5.2±2.1 (n=7). High CSA levels were found in leukemic sera 20-30 days post BMT, 27±4.3 CFU-MK, (n=7). Conditioning for BMT included chemotherapy and fractionated total body irradiation (TBI,1200 cGy). AA sera contained MK-CSA prior to BMT, 35±4.7 CFU-MK (n=6) with no increment following BMT. Serum from a victim who was accidentally exposed to lethal irradiation in an atomic reactor, and was treated with BMT, contained highly potent MK-CSA (CFU-MK= 118±6.6). Similar CSA was found in lethally irradiated dogs (CFU-MK= 156±14.2). No elevation of GM-CSF, IL3, IL-6, IL-1 beta, or EPO were detected. Hence, despite a similar degree of thrombocytopenia, lethal irradiation stimulates high levels of potent MK-CSA compared to carboplatin or chemotherapy and TBI.

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IN VITRO STUDIES OF STEM CELL FACTOR (SCF) AND INTERLEUKIN-11 (IL-11) IN NORMAL AND "PRELEUKEMIC" HAEMATOPOIESIS

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Haematopoietic growth factors are more and more being introduced into cancer therapy, and G-CSF or GM-CSF have been shown to effectively stimulate granulopoiesis during leukopenia caused by chemotherapy or in primary bone marrow disorders like myelodysplastic syndromes (MDS). Erythropoetin (EPO) is able to enhance erythopoiesis in tumor patients, but more or less only in cases with normal or decreased endogenous EPO level. No factor is available for the in vivo stimulation of megakaryopoiesis. Using a soft agar haematopoietic progenitor cell assay, we therefore investigated additional recombinant cytokines for their potential to stimulate haematopoiesis in normal persons and defective haematopoiesis in patients with MDS. Various cytokines alone and in combination were included in our test system: stem cell factor (SCF; Amgen), IL-3, IL-6, IL-11 (Schering Plough), G-CSF, GM-CSF and EPO. Regarding granulopoiesis, SCF alone or in combination with other cytokines showed significant stimulation, while IL-11 demonstrated no effect. IL-11 or SCF given alone was not able to significantly stimulate erythropoiesis, but the combination of SCF and EPO was highly effective. A significant stimulation of megakaryopoiesis was shown with IL-11 alone. This induction of megakaryopoiesis was expressed even more markedly in combination with IL-3, but not with IL-6 or SCF.
Our results demonstrate that IL-11 might be an interesting factor for the in vivo stimulation of megakaryopoiesis, while the combination of SCF and EPO holds promise to influence erythropoiesis even in patients not responding to EPO alone.

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PLATELETS, GRANULOCYTES AND HAIR GROWTH FACTOR EFFECT OF THE NEW IMMUNOMODULATOR AS101 IN CHEMOTHERAPY TREATED LUNG CANCER PATIENTS

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AS101 (ammonium trichloro (Dioxyethylene-0,0' tellurate)) a novel immunomodulator, has shown an anti-tumor effect and immune stimulation in animal studies. In human phase I study it significantly increased IL-2, IL-2 receptor, interferon and TNFα. This compound, given intravenously thrice-weekly, was added in a randomized protocol to chemotherapy, consisted of carboplatin and VP-16 in 61 non small cell lung cancer patients. Results have shown significant sparing from hair loss, neutropenia and thrombopenia in the AS101 treated group. This was accompanied by parallel elevation of CSF and IL-6. Response rate in the AS101 treated group was better than the chemotherapy only group.

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LACK OF PROGNOSTIC VALUE OF EGF RECEPTOR IN A SERIES OF 229 T1 / T2, N0 / N1, M0 BREAST CARCINOMAS WITH WELL DEFINED PROGNOSTIC PARAMETERS. A DEFINITIVE ANALYSIS

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The prognostic value of EGF-R was prospectively assessed in a series of 229 clinical T1/T2, N0/N1 breast carcinomas diagnosed between May 1987 and October 1989. Median age was 56 years, and 37.6 % of the patients were not menauposed. There were 41.9 % of T1, 58.1 % of T2, 50.2 % of pT1 and 49.8 % of pT2. Histological axillary lymph node status was negative in 50.6 %. Loco-regional treatment was represented by conservative or radical surgery, associated with post-operative radiotherapy. Adjuvant hormonotherapy was given in 50.2 % of the cases, with respect to 9 % for chemotherapy. A binding assay for EGF-R was performed using a single saturating concentration of ^{125}I-EGF incubated with membrane preparations in the presence or absence of unlabelled EGF. A median value of 3 fmol EGF binding capacity per mg of membrane was selected as the threshold value. With a median follow-up of 34 months the 3-year overall and disease free survivals are respectively 92 % and 88 % for EGF ≥ 3, and 91 % and 86 % for EGF-R > 3 without any significant difference, even when comparing axillary lymph node status. We did not succeed in finding an EGF-R cut-off value which might be significant in univariate analysis.The multivariate analysis showed that pT (0.000), pN (0.04), Scarff-Bloom grade (0.04) were the only powerful predictors of disease free survival.