22 pts with AJCC stage III MM were treated with ID IFN-α2b (3 MUI to 10 MUI s.c. for six wks followed by 10 MUI/TIW × s.c. for 48 wks), and *c*) 20 pts recurring after LD IFN-α were treated with ID IFN-α (10 MUI/TIW s.c for 1 year). Treatment started within 30 days after surgical treatment of primary lesion for *a* + *b* and local recurrence or node dissection for *c*.

Results: *a*) Planned 3 yrs IFNα-2b therapy was completed in 38 (44%) pts (median DFS 30 months, range 2–62). Relapses occurred in 26 pts (13 local or in-transit recurrence, regional lymph nodes and 6 distal metastasis). Treatment was suspended for toxicity in 6 (7%) pts; a dose reduction was carried out in 7 (8%) pts. None of the 13 deaths registered were treatment-related. *b*) Treatment was completed in 11 (50%) pts. None of pts discontinued induction treatment; in 3 pts, doses were reduced for neurological toxicity (WHO grade 3). Main toxicity was flu-like syndrome, haeamatological, hepatic, gastrointestinal (WHO grade 2). *c*) Seventeen (85%) pts recurred during treatment with WHO grade 34 toxicity occurring in 6 (30%) pts.

Discussion: Our preliminary results suggest that *a*) positive outcome might be obtained using LD IFNa doses; *b*) ID regimen seems were tolerated and feasible (follow-up is still too short to draw any conclusion about its efficacy); and *c*) escalation of doses (from LD to ID) in MM pts previously treated with LD IFNa is clearly ineffective.

1526 PUBLICATION

Polyenzyme preparations interrupt the autocrine loop of TGF-beta production in melanoma cells by conversing alpha2Macroglobulin (a2M) into the fast-form which binds TGF-beta irreversible

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Integrins are cell surface molecules, which mediate cell-matrix and cell-cell adhesion. TGF-beta increases av integrin expression on several cell types including melanomas at both, the protein- and mRNA-level. alpha2M (an inhibitor of proteinases) binds in the fast-form irreversibly TGF-beta. Wobenzym® (pancreatin, bromelain, papain, trypsin and chymotrypsin) has been successfully used in adjuvant tumor therapy. In this study we examined av integrin expression and TGF-beta synthesis (ELISA and RT-PCR) in 6 human melanoma cell lines established from primary tumors and metastatic tissues. All cell lines express av integrin and produce TGF-beta in latent (6/6) or active (3/6) form. Treatment up to 24 hrs with 2 ng/ml TGF-beta enhances av integrin expression in all cell lines investigated. Incubation with Wobenzym® has reduced the expression of av integrins after 8 hrs earliest to 26–66%. This downregulation of av integrins (ELISA) was preceded by a reduction of TGF-beta mRNA (38–89% of the control). We propose, that Wobenzym® and its constituents reduce the production of TGF-beta by converting a2M into the fast-form, which binds to TGF-beta, thus interrupting the autocrine loop of TGF-beta production.

Prevention of treatment related side effects

1527 POSTER

Biochemical detection of heart failure after anthracycline chemotherapy

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Anthracyclines can provoke evident heart failure (up to 20% of pts) until 15 years after their discontinuation. Considering only a decrease in left ventricular ejection fraction (LVEF) without symptoms, the prevalence of cardiotoxicity is higher. Brain natriuretic peptide (BNP) is a cardiac hormone released by ventricle in response to increased intracardiac volume or pressure. BNP plasma concentration raises in presence of overt heart failure appearing to be a useful and cost-effective marker of LVEF also in asymptomatic pts [Lancet 1998; Vol 351 (3): 9–13]. Fourteen breast cancer pts (median age 62 ys) were treated with anthracycline (Doxorubicin up to 300 mg/sm). Eligible criteria were no significant history of heart disease or uncontrolled hypertension. Before the treatment each pts underwent a LVEF evaluation by multiple gated acquisition (MUGA) cardiac blood pool scan; pts with LVEF <50% were not treated. We evaluated BNP levels during treatment using Shionoria kits (Shionogi Asaka Japan). These kits use two different monoclonal antibodies coated in a solid-phase (the second radiolabeled with iodine 125) that recognise two sterically remote sites. The beads retain only the absorbed antibody/antigen/tracer complex and the amount of radioactivity is proportional to amount of BNP present in the sample. Normal value is <18 ng/mL.

Our data show that BNP levels raise consensually to decrease in LVEF evaluated by MUGA. Two pts showed, at entry study, a normal BNP level at rest but they had raised BNP levels immediately after exercise stress test carried out before chemotherapy. The BNP levels at rest of the same two pts remained in normal range also after doxorubicin levels of 150 and 300 mg/sm. BNP levels are inversely related to LVEF; its simple blood determination could replace the MUGA evaluation. The BNP increase after exercise stress test, might be useful to identify a pts subgroup with higher heart vulnerability to anthracyclines. A longer follow-up will better explain these data.

1528 POSTER

Evaluation and quality of life in a clinical trial with non-random dropout assessing the effect of epoetin alfa on cancer-related anemia

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Purpose: A joint mixed effects and dropout model for longitudinal studies with non-random dropout was used to analyze quality-of-life (QOL) endpoints in a randomized, placebo-controlled clinical trial.

Methods: Patients receiving non-platinum chemotherapy having a hemoglobin (Hb) 10.5 g/dL or less, or a decline in Hb of 1.5 g/dL or greater were randomized to epoetin alfa or placebo. Study duration was variable across subjects, based upon the expected number of chemotherapy cycles per subject. QOL was assessed prior to treatment, at 4 and 16 weeks, and at the time of discontinuation using 3 QOL instruments: the Functional Assessment of Cancer Therapy – Anemia (FACT-An), Cancer Linear Analogue Scale (CLAS), and the SF-36. Seven QOL scales from within these questionnaires were identified a priori as primary endpoints: the FACT-G, FACT-An Fatigue, CLAS Energy, CLAS Daily Activities, CLAS Overall QOL, SF-36 physical component scale, and the SF-36 mental component scale.

Results: 96 of 248 epoetin alfa-treated (39%) and 61 of 124 placebo (51%) patients discontinued the trial early. All 7 primary QOL measures exhibited lower QOL scores for subjects who discontinued the study earlier than anticipated, indicating a non-random dropout process. Accounting for this non-random dropout process, patients receiving epoetin alfa had significantly better QOL scores over a 16-week period relative to placebo for the FACT-G, FACT-An Fatigue, CLAS Energy, CLAS Daily Activities, and CLAS Overall QOL (all p-values < 0.05). There was a non-significant positive difference in favor of epoetin alfa in the 2 summary SF-36 scales.

Conclusion: In a longitudinal analysis incorporating a non-random dropout mechanism, a positive treatment effect for epoetin alfa on cancer-specific QOL domains was established, especially in the areas of anemia-related fatigue, loss of energy, and a reduction in daily activities.

1529 POSTER

An evaluation of potential neuroprotective effect of reduced-glutathione (GSH) on oxaliplatin (OXA) based chemotherapy in advanced colorectal cancer patients

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Purpose: We performed a randomized placebo-controlled trial to assess the efficacy of GSH in the prevention of OXA-induced neurotoxicity.

Methods: 20 patients (pts) after failure of first-line treatment, M/F 9/11, median age 59 y (range 40–76), ECOG = 0–1, treated with OXA 100 mg/m^2 iv 2-h infusion d1, 6S-leucovorin 250 mg/m^2 plus 5fluorouracil 1.5 g/m^2 continuous infusion for 2d q 2wks, were randomized to receive GSH 1.5 g/m^2 iv or normal saline solution. Neurotoxicity evaluation according NCI-CTC and electrophysiologic investigations have been perfomed at baseline, after 4 (OXA dose, 400 mg/m^2), and after 6 (OXA dose, 600 mg/m^2) cycles.

Results: In 17 evaluable pts 4 PR (24%, 95% I.C. 3.36%–43.69%), and 6 SD (34%) were observed. After 4 cycles in the GSH arm 4/8 pts