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

experienced grade 1 and 2/8 pts grade 2 neurotoxicity and similarly in the placebo arm 6/12 pts grade 1 and 1/12 pts grade 2. After 6 cycles, in the 12 pts evaluable, in the GSH arm 3/5 pts experienced grade 2 and no pts grade 3 neurotoxicity while in the placebo ann 3/7 pts grade 1 and 2/7 grade 3. After 4 cycle the neurophysiologic evaluation showed no changes in mean latency and in the sensory amplitude potentials both in the GSH arm and control arm.

Conclusion: The preliminary results do not provide evidence that GSH has a protective effect on the OXA-induced neuropathy. Further analysis will be performed at the end of the study after an enrollment of at least 15 pts for each arm.

1530 POSTER

Equivalent effects on functional status and hematologic indicators of epoetin alfa in patients (PTS) treated with platinum (P) or non-platinum (NP) chemotherapy (CT) regimens independent of disease response

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Purpose: To compare hematologic response and functional status in anemic pts treated with either P or NP CT and concurrent epoetin alfa.

Methods: Open-label multicenter trial of anemic (hemoglobin [Hb] 11 g/dL or less) cancer pts receiving CT. Epoetin alfa was dosed at 10,000 international units (IU) SQ TIW (increased to 20,000 IU if necessary, based on Hb response at 4 weeks) for a maximum of 16 weeks. Activity, energy levels, and overall quality-of-life (QOL) scores were evaluated by linear analog scale assessment (LASA), a pt-reported survey instrument.

Results: Of 2370 patients enrolled, 2289 (808 P; 1481 NP) were eligible for efficacy analysis. Mean Hb at baseline (BL), defined as 1 month prior to study, was 9.3 g/dL for P and NP groups, and increased significantly ($P < 0.001$) to 11.4 g/dL and 11.2 g/dL, respectively. Transfusion (TF) requirements similarly decreased significantly for both groups over the 4-month study period:

Month	P		NP	
	%TF	mean units	%TF	mean units
BL	26.2	.89	29.8	1.07
1	23.9	.61†	18.6*	.46*
2	14.7*	.39*	11.1*	.30*
3	8.1*	.21*	8.0*	.21*
4	5.5*	.13*	4.7*	.17*

*Significantly different ($P < 0.001$) less than baseline.; †Significantly different ($P < 0.05$) less than baseline.

LASA scores increased significantly ($P < 0.001$) from baseline for both P and Np groups. Mean increases (mm on LASA scale) from baseline to last value for P/NP groups were: energy 11.4/11.6; activity 11.0/11.2; overall QQL 10.2/9.5. Improvements in LASA scores were significant ($P < 0.05$) for pts who had increases in Hb, with greater Hb increases yielding greater improvements. Increases in LASA scores were independent of CT regimen or degree of CT-associated disease response.

Conclusion: Epoetin alfa, when administered to cancer patients receiving CT, significantly increased Hb and reduced TF requirements, as well as improved activity, energy, and overall QQL, equally well with either P or NP regimens. Greater Hb increases were associated with greater improvements in functional status of both patient groups. Comparable benefits were noted independent of disease response to CT. These results support use of epoetin alfa to maximize functional status of anemic pts receiving either P or NP CT regimens.

1531 PUBLICATION

Clinical, ultrasonographic, hysteroscopic, and histopathological evaluation of the endometrial changes in women with breast cancer (BC) submitted to adjuvant tamoxifen (TMX)

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Purpose: TMX is the most used drug in adjuvant therapy of BC. Indications for its use are not restricted to postmenopausal patients with advanced BC but included almost all patients at any stage of the disease and lately it has been proposed as chemoprevention for those with increased risk of its development. TMX is reported as risk factor to development endometrial cancer. The scope of this study is to approach the side effects of TMX on endometrium of patients with BC.

Methods: 56 patients from the Cancer Institute of Ceará, in use of TMX for 3–77 months; 38 (68%), postmenopausal. Age: 33–88 years old. The patients were evaluated as to age, menopausal status, length of treatment and gynecological complaints. All patients were submitted to pelvic transvaginal ultrasound (PTUS), 11 to hysteroscopy with biopsy.

Results: 5 (8.9%) patients with transvaginal bleeding (TB). Considering a cut-off of 5 mm for the endometrial thickening on PTUS, 30 (53.6%) had endometrial thickening, 21 postmenopausal and 9 premenopausal with maximum thickness of 38 mm. Cystic degeneration was the most commom finding. 11 patients underwent hysteroscopy (36.7% with thickened endometrium), 10 (91%) with cystic changes. Histopathological findings: atrophy, 9 (82%); secretory endometrium, 1 (9%); complex hyperplasia without atypia (CHWA), 1 patient. Hysterectomy and bilateral salpingo-ophorectomy were carried out in 3 patients (ovarian cyst, tickened endometrium and ovarian cyst, and the last for a persistent TB). 2 had secretory endometrium and the last, CHWA.

Conclusion: Patients with BC using TMX must have systematic follow-up with clinical evaluation and PTUS, before starting the treatment and every six months. Attention must be paid to gynecological symptoms, specially TB. When the endometrium becomes progressively thicker (>5 mm), with abnormal aspect or in the event of gynecological findings, hysteroscopy with biopsy is safer and will provide more information to the follow-up. Age, menopausal status, extent of TMX use, and endometrial thickness have not shown significant statistical differences.

1532 PUBLICATION

Total prevention of taxoid-induced alopecia by a new model of cold cap (dignitana)

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Purpose: Alopecia is one of the most common and emotionally distressing side effects of cancer chemotherapy. Scalp cooling prevents alopecia but a continuos drop in temperature is difficult to maintain since the ice-cap must be changed after 30–45 minutes. Since many regimes last for several hours the ice-cap must be changed several times. The present methods are afflicted with various discomforts for the patients. We have developed a computer-controlled cooling system, which allows continuos cooling of the scalp during the whole treatment time (DIGNITANA).

Mechanisms behind the reduction of hair loss during local hypothermia is not completely known but may include decrease in the metabolic rate, reduction of scalp circulation and reduction of the temperature-dependent cellular uptake of the drugs.

Method: 3 patients with ovarian carcinoma were treated with Paclitaxel 135–175 mg/m^2 infusion (4 h). The cap (DIGNITANA) was applied on wet hair 30 minutes before, during and 30 minutes after the infusion. 2 patients (controls) were treated with Paclitaxel but without cold-cap. In addition 3 patients using (DIGNITANA) with breast carcinoma were treated with Docetaxel 100 mg/m^2 1-hour infusion, 2 patients with FEC, and one patient with CNF. Loss of hair was estimated (VAS scale 1–10) by two observers independently. Patient discomfort was assessed by the patients.

In Paclitaxel-treated patients (5 with cold-cap, 2 without) lactate, glucose, pyruvate and glycerol were analysed continuously by using a micro-dialysis probe subcutaneously both in the scalp and the abdominal wall.

Results: In Paclitaxel-treated patients total alopecia (VAS = 10) was noticed for the control patients. In the patients treated with the cold-cap the median (range) VAS value regarding the hair loss was 1.3 (1–3). The discomfort was initially higher 3 (2–5) and after 10 minutes 1.5 (1–3). In Docetaxel-treated patients the hair loss was estimated 1.3 (1–3) and the discomfort 2.6 (0–5), 1 (1–2). In FEC-patients the VAS values were 2.5 (1–4), 2 (1–3) and 1 (1–1)

The glucose/lactate ratio was lower in the hypothermic scalp than in the normothermic scalp or the abdominal wall.

Conclusion: Continuous computerised hypothermia by using cold-cap (DIGNITANA) during treatment with taxoids and FEC prevents alopecia with hardly any discomfort.