1521 PUBLICATION

Intratumoural cisplatin/epinephrine injectable gel provides palliative tumour control for patients with metastatic melanoma

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Purpose: Patients with malignant melanoma who have dermal metastases and no clinically problematic visceral disease are good candidates for local therapy. We evaluated a novel chemotherapeutic, cisplatin/epinephrine injectable gel (CDDP/epi gel), designed to deliver high concentrations of drug for extended periods after direct intratumoral injection to patients with clinically troublesome skin, lymph node, and soft tissue melanoma.

Methods: 28 patients who had failed one or more previous therapies received weekly intratumoral CDDP/epi gel (0.5 mL/cm^3 tumor volume; 0.5 mL contains 2 mg CDDP and 0.05 mg epi), for up to 6 treatments in 8 weeks, then were followed at least 4 weeks. Evaluations included response of all tumors treated and response and achievement of patient benefit (e.g., pain control, improved wound care) in a prospectively designated clinically most troublesome tumor (MTT).

Results: A total of 25 patients with 107 lesions received a median of 6 treatments; median cumulative dose of 41.6 mg CDDP (range 10.8–204 mg) was given. Overall, 44% (11 of 25) patients experienced objective MTT responses (≥50% decrease tumor size); 4 of these 11 had additional therapy with other modalities within 28 days of response onset. Mild/moderate vomiting and nausea occurred less frequently (21%) than would be expected with intravenous cisplatin. A clinical benefit was achieved by 36% of all patients, and 45% of responders.

Conclusion: Intratumoral CDDP/epi injectable gel provides a new therapeutic approach for local control and management of symptoms in melanoma patients with skin and soft tissue metastases.

1522 PUBLICATION

Combined chemotherapy in disseminated skin melanoma

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Purpose: A new chemotherapy regimen with Nidran (ACNU) + Dacarbazin (DTIC) + Cisplatin (cis-DDP) was studied in 32 patients with disseminated skin melanoma, without previous chemotherapy.

Methods: ACNU was used at the dose 1 mg/kg IV day 1, DTIC – 250 mg/m^2 IV days 1–3, cis-DDP – 100 mg/m^2 IV day 3. Intervals between courses-4 weeks. Treatment response was compared with O^6-alkylguanine-DNA-alkyltransferase (AGAT) level in lymphocytes. 15 patients had soft tissues metastases only, 17 patients had visceral metastases.

Results: Treatment response was assessed in 32 patients that received 116 chemotherapy cycles. Complete Response (CR) + Partial Response (PR) were obtained in 40.5% patients, Stable Disease (>3 months) – in 28.1% patients. Treatment response duration was 6–42 + months. The treatment response was achieved in metastases to soft tissues only (66.6%), lungs (50%), liver (14.2%), brain (66.6%).

Correlation of AGAT in lymphocytes and treatment response was detected. CR and PR is more often achieved in low AGAT level.

Conclusion: The combination of ACNU + DTIC + cis-DDP is highly efficient in disseminated melanoma. AGAT level can predict response of ACNU + DTIC + cis-DDP in malignant melanoma.

1523 PUBLICATION

Results of a randomized phase II study of two schedules of bryostatin-1 in patients with malignant melanoma: Experience with the multivariate stopping rule

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Aim: Bryostatin was anticipated to be cytostatic rather than cytotoxic; we wished to determine which of two schedules of bryostatin was the most promising in terms of efficacy and tolerability utilizing a multivariate stopping rule (Zee 1999) based on proportions of both response (OR) and early progression (EP) within 8 weeks.

Methods: 34 patients (pts) with advanced or metastatic melanoma were randomly assigned to arm A (bryostatin 25 μg/m^2 continuous infusion (CI) over 24 hrs weekly) or arm B bryostatin 120 μg/m^2 (CI) over 72 hours every 2 weeks. In stage I, an arm would be considered inactive if OR was 0%; if 1 pt had OR but 7 or more had EP; or if >8 pts had EP irrespective of the number of OR,s.

Results: 32 chemotherapy naïve pts were evaluable for toxicity and 30 for response (15 each in arm A and B). Median age was 58 yrs (25–77 yrs); male pts = 18; performance status was 0 (15 pts), 1 (14 pts) or 2 (3 pts); 17 pts had had prior immunotherapy; most common sites of disease were lung (19 pts), nodes (15 pts) and liver (10 pts); baseline demographics were generally well balanced in the two arms although pts in arm A were more likely to have had prior immunotherapy and less likely to have lung metastases. 87% of pts in arm A received at least 90% of planned dose intensity compared to 77% in arm B. Comparative drug related toxicity arms A: B: myalgia 33% vs. 65%; lethargy 40% vs. 29%; nausea 27% vs. 12%; headache 13% vs. 24%. Hematologic toxicity was mild in both arms. No responses were seen in either arm; 12 pts experienced early progression in arm A and 11 pts in arm B.

Conclusions: Bryostatin appears to have little activity in pts with advanced/metastatic melanoma even when a multivariate stopping rule is incorporated; more prolonged infusions of bryostatin are associated with more myalgia and are less well tolerated than shorter infusions.

1524 PUBLICATION

Adjuvant BCG for early-stage melanoma: A prospective randomized uni-institutional study

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Introduction: there has been in the past decade some enthusiasm on immunotherapy with bacille Calmet-Guérin (BCG), that resulted from evidence of antimelanoma activity observed in experimental and some clinical trials. At that time, oral BCG was tested in the adjuvant setting on localized melanoma at our institution, in a prospective randomized study.

Patients and Methods: this was a 2 arm single-institution prospective randomized trial. To be elegible for the study patients had to have proven localized melanoma of the skin. Patients were stratified for Breslow depth (BD), Clark stage and presence of ulceration. Treatment arm received oral BCG at a dose of 500 mg t.i.w. for 1 year. Control arm received no treatment. Main end points were disease free and overall survival.

Results: From Jan/83 to Nov/87, 101 patients were included in this trial, 52 in the BCG arm and 49 in the control group. 33 (67%) patients in the control and 43 (82%) in the BCG arm had tumors with BD over 0.76 mm. Both groups were well balanced for age, gender and primary site. Survival rates were calculated with Kaplan-Meyer product limit estimator and log-rank test was used for comparison of the curves. Multivariate analysis was performed using Cox proportional hazards models.

With a median follow up of 8 years (range 0 to 14), median survival time was not achieved for both groups. However, 5 and 10 year overall survival (OVS) was 71.4 and 64.2% and 87.3 and 69.5% for BCG and control arms, respectively ($p = 0.45$). Disease free 5 and 10 years survival (DFS) was 59.5 and 56.5%, and 64.8 and 47.5% for BCG and control groups, respectively ($p = 0.99$). No grade 3 and 4 toxicity was observed. Multivariate analysis disclosed sex and Clark level as independent prognostic factor to OVS and DFS, respectively.

Conclusion: In this prospective randomized trial BCG failed to prolong survival or delay recurrence in early-stage melanoma.

1525 PUBLICATION

Adjuvant treatment with interferon-α in melanoma stage II–III: Experience of melanoma cooperative group

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Background: Interferon-α (IFN-α) has been shown to improve disease-free survival (DFS) and overall survival (OS) in stage II–III patients (pts) with malignant melanoma (MM), using both high- (HD) and low- (LD) IFN-α doses. However, HD treatment has been widely reported to be associated with considerable toxicity and poor quality of life. In addition, preliminary results of ECOG 1690 trial showed no differences in OS between HD and LD. We report our experience with LD and intermediate doses (ID) of IFN-α2b.

Patients and Methods: *a*) since 1993, 86 pts with MM AJCC stage II–III were treated with IFN-α2b (3 MUI/TIW s.c. for 3 yrs); *b*) since April 1998,

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