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,