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503 Phase I radioimmunotherapy (RIT) study of 90Y-CC49 monoclonal antibody (MAb) therapy in patients with advanced non-small cell lung cancer (NSCLC)

Francisco Robert

Ruby Meredith

Michael Khazaeli

Charles Russell

William Grizzle

See next page for additional authors

Authors

Francisco Robert, Ruby Meredith, Michael Khazaeli, Charles Russell, William Grizzle, John Newsome, and Mansoor Saleh

501 Is smoking a confounding factor when evaluating cancer treatment? Effects of smoking on radiation-induced pneumonitis

S. Johansson, L. Bjermer, L. Franzén, R. Henriksson. *Depts of Oncology, Umeå University, Umeå, Sweden, Depts of Oncology, Umeå Lungmedicine, Trondheim, Norway*

Background: Previously we have shown by using broncho-alveolar-lavage that ongoing smoking suppressed the *early* inflammatory response of the lung after irradiation.

Aim: To investigate the influence of smoking on the development of radiation-induced pneumonitis in patients treated with radiotherapy for breast and oesophagus cancer.

Methods: This is a retrospective study on 405 women diagnosed with primary localized breast cancer, and 201 oesophagus cancer patients. All were treated with radiotherapy. Information was recorded on smoking habits, radiotherapy and reported pneumonitis. Radiation-induced pneumonitis was defined as a combination of *both* roentgenographic infiltrate in the irradiated lung field, and clinical symptoms such as non-productive cough and dyspnoea.

Results: Six breast cancer patients had spontaneously reported pneumonitis and all of them were non-smokers. One was a former smoker who had quit smoking more than two years prior to irradiation. Eight of the oesophagus cancer patients had spontaneously reported radiation induced pneumonitis and they were all non-smokers, except one, who was a pipe-smoker. None of the patients who were cigarette smokers developed pneumonitis after irradiation.

Conclusion: The results support clinical and experimental observations that smoking depresses the frequency of radiation induced pneumonitis and tumour growth in animals. It is proposed that ongoing smoking could be a confounding factor when evaluating effects of cancer treatment.

502 Oral ubiquinone (q10) intake reduces the *in vivo* radiosensitivity of small cell lung cancer (SCLC)

E.L. Lund, B. Quistorff, P.E.G. Kristjansen. *University of Copenhagen, Denmark*

The effect of the lipid soluble antioxidant Q10 (ubiquinone) on the *in vivo* response of SCLC tumors to single-dose radiotherapy was examined. Many cancer patients use oral Q10 as a self-prescribed adjuvant to their therapy. Our experimental findings are indicative that a potentially harmful interaction, leading to diminished local tumor control, may occur in patients undergoing radiotherapy. The human SCLC line CPH 54A, which is sensitive to low doses of gamma irradiation both *in vitro* and *in vivo,* was grown subcutaneously in nude mice. When tumor growth was established, groups of mice received either 10, 20 or 40 mg/kg Q10 in 0.03 ml soy oil intragastrically daily on 4 consecutive days. Controls received either 0.03 ml of pure soy oil at the same schedule or nothing. Three hours after the last dose half of the tumors in each group received a single radiation dose of 5 Gy, using a 300 kV therapeutic unit. Changes in the tumor growth following treatment was analyzed according to the Gompertz algorithm using the software program GROWTH. In a parallel experiment, mice were sacrificed 3 hours following the last dose and tumor, heart and blood was analyzed by reverse-phase HPLC for the content of Q10 and endogenous (murine) Q6. Treatment with Q10 or soy oil alone had no effect on tumor growth compared with untreated controls. Groups of tumors that received Q10 and radiotherapy had a significantly lower specific growth delay (SGD) than the radiotherapy-only groups. This effect was significant at 40 mg/kg and borderline at 20 mg/kg, wereas at 10 mg/kg no radioprotection was seen. Interestingly, when similar studies were performed with a water-soluble oral antioxidant (ascorbic acid) no radioprotection of the tumors was observed. The radiobiological implications of this discrepancy are currently under further investigation. We conclude that systemic Q10 treatment significantly reduces the response to single dose tumor irradiation in heterotransplanted SCLC tumors. The magnitude of this potentially adverse effect is dose dependent. We feel that the present experimental data justify a warning against concurrent use of Q10 during radiotherapy. Prospective clinical testing is not warranted in this particular case, since the likelihood of clinical adversity is not balanced against a hypothetical benefit.

503 Phase I radioimmunotherapy (RIT) study of ^{90}Y-CC49 monoclonal antibody (MAb) therapy in patients with advanced non-small cell lung cancer (NSCLC)

F. Robert, R.F. Meredith, M.B. Khazaeli, C. Russell, W. Grizzle, J. Newsome, M. Saleh, A.F. LoBuglio. *Univ. of Ala. at Bham., Comprehensive Cancer Center, Bham, AL, USA*

We conducted a phase I dose-escalation study of ^{90}Y-labeled anti-TAG-72 MAb CC49 in patients (pts) with stage IV NSCLC. The high frequency of TAG-72 expression in NSCLC and lack of significant reactivity with normal adult tissues provide a rationale for the use of a radiolabeled MAb as a therapeutic strategy in these tumors. ^{90}Y is a β-emitting radionuclide and ideally suited for localized radiation delivery. Pts underwent biodistribution and whole body kinetic studies using ^{111}IN-C49 prior to RIT. Eligible pts received a single IV dose of ^{90}Y-CC49 at a starting dose of 8 mCi/m^2, with an increment of 3 mCi/m^2 at each subsequent dose level. Pts received four doses of recombinant α-2β interferon (3 $\times$ 10^6 U, subcutaneously) on days – 4 to 1 in order to upregulate TAG-72 expression. A total of 15 pts have been treated with doses ranging from 15.1 to 30.8 mCi (8–14 mCi/m^2). Seventy-five percent of these pts had at least one site of disease imaged following ^{111}IN-CC49. Both interferon and ^{90}Y-CC49 were tolerated well, without significant non-hematological toxicity. Reversible myelosuppression has been observed. Two grades 3–4 thrombocytopenia, and one grade 3 neutropenia, have been observed in two of four pts treated at 14 mCi/m^2. Six pts (43%) experienced $\geq$ grade 2 anemia at doses of $\geq$11 mCi/m^2. Seven pts developed human antimouse antibody 3–4 weeks after treatment. Five pts demonstrated transient stabilization of disease. Our plan, once the maximum tolerated dose has been reached, is to consider dose escalation of ^{90}Y-CC49 in conjunction with two metal chelators (EDTA and DPTA). This approach would significantly increase excretion of ^{90}Y, reduce marrow toxicity and allow further dose escalation into clinically therapeutic ranges.

504 Early vs late bifractionated chest irradiation concurrently with chemotherapy in limited disease (LD) small-cell lung cancer (SCLC) (Preliminary results)

E. Samantas, G. Fountzilas, A. Athanassiades, N. Pavlidis, C. Nikolaides, E. Panousaki, C. Kalofonos, E. Tsiakopoulos, E. Kosmas, C. Kiamouris, D. Skarlos. *HeCOG Data Office, Athens, GR*

The aim of this randomized study was to evaluate the impact of the early vs late bifractionated chest irradiation in combination with chemotherapy for LD, SCLC patients. Since February 1994, 36 patients with LD, SCLC were randomized to receive chemotherapy consisting of Carboplatin 6 $\times$ (AUC) I.V. day 1 and Etoposide 100 mg/m^2 I.V. days 1, 2 and 3, every three weeks for a total of 6 cycles, with chest irradiation (1.5 Gy twice daily, total 45 Gy) concurrently either with the first (Group A) or the fourth (Group B) cycle of chemotherapy. Patients with complete response also received prophylactic cranial irradiation after the end of the combined treatment. Thirty-six patients have been randomized so far, 14 (39%) in Group A and 22 (61%) in Group B.

Results: (Group A vs Group B): Overall responses 71% (10 pts) vs 82% (18 pts), complete responses 36% (5 pts) vs 55% (12 pts), partial responses 36% (5 pts) vs 27% (6 pts). One patient (Group A) had stable disease and 6 patients (17%) are too early to be evaluated. With a median follow-up of 17.5 (range 0.03–33.48) months, time to progression was 8.92 (range 0.69–12.75) vs 12.10 (range 0.03–26.79) months and the median survival 14 months (range 0.69–20.56) vs 16.8 (range 0.03–33.48) months. Grade III, IV toxicities included leucopenia 14% vs 9%, thrombocytopenia 7% vs 9% and anaemia 7% vs 9%. Alopecia was almost universal.

In conclusion, the combination of chemotherapy concurrently with chest radiotherapy is a very effective treament with acceptable toxicity in patients with LD, SCLC. It is too early for conclusions regarding the timing of chemotherapy.