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Final report of a phase I radiation dose escalation study in patients with inoperable/unresectable non-small cell lung cancer: predictors for radiation pneumonitis

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Purpose: With maturating of a conformal radiation dose escalation study in non-small cell lung cancer (NSCLC), the purpose of this report is to report the observed lung toxicities and to examine predictive factors associated with them.
Materials and methods: Eligibility included newly diagnosed/recurrent stage I-III inoperable/unresectable NSCLC. The study used a standard phase I design, with dose chosen and escalated within five bins based on estimated normal tissue complication probability (NTCP) according to lung effective volume. The starting NTCPs ranged 1 to 10% with starting doses of 63 to 84 Gy. Since 1997, stage III patients received neoadjuvant cisplatin and vinorelbine. Radiation pneumonitis was determined with a SWOG based grading system, involving a team of radiation oncologists, medical oncologists, and a pulmonologist.
Results: A total of 122 patients were consented for the study between 1992 and 2000. After excluding cases those taken off study due to various reasons and those who died within 6 months from the start of radiation, 92 patients who received 63–102.9 (median 76) Gy were included in this analysis. Seventeen patients received chemotherapy. With median follow-up of 97 months, none developed grade 4 and 5 lung toxicity. Seventeen patients had grade 2–3 radiation pneumonitis. Sixteen patients had symptomatic fibrosis, 11 (69%) of them evolved from grade 2–3 pneumonitis. Univariate models showed T stage, gross tumor volume, total lung volume, tumor dose, mean lung dose (MLD), volume receiving 13, 20, 30 Gy and NTCP were significantly ($p < 0.05$) associated with pneumonitis. Results from multivariate analysis, however, revealed only V13 ($p = 0.014$), V20 ($p = 0.012$), MLD ($p = 0.005$), and NTCP ($p = 0.009$) were independent predictors. Using cut-offs of 30%, 20 Gy, and 15% for V20, MLD and NTCP, the sensitivity, specificity, and positive and negative predictive values were 50%, 90–93%, 50–62% and 90%, respectively.
Conclusions: Tumor dose up to 103 Gy can be delivered with minimal severe lung toxicity if lung dose is limited. Moderate radiation pneumonitis is not associated with prescription dose, but with lung dosimetric parameters and NTCP. The commonly used dosimetric predictive cut-offs have excellent negative predictive value, and may be safely used in the future study or practice to select patients for individualized high dose radiation.

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Vitamin E and pentoxifylline protect the development of radiation-induced pulmonary fibrosis in rats

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Background: Studies have shown that radiation-induced pulmonary fibrosis is a dynamic process characterized by a constant remodeling of fibrous tissue and long term fibroblast activation. Therefore biological modifiers have been studied to manipulate this process to minimize the development of radiation-induced fibrosis. In this study we created the hypothesis that vitamin E can modify the development of radiation-induced fibrosis acting as an anti-oxidant. In addition we searched if combination of vitamin E with pentoxifylline is more effective on modifying the hypoxia and the oxidative stress. We also searched if modification of hypoxia with pentoxifylline alone has any impact on the development of radiation-induced pulmonary fibrosis.
Material and methods: Twenty-four female Wistar Albino rats were randomized into 4 experimental groups. The first group of rats (Group A), had irradiation to whole thoracic region. The second group of animals (Group B) had thoracic irradiation with pentoxifylline. The third group of animals (Group C) had thoracic irradiation and vitamin E. The fourth group of animals (Group D) had vitamin E and pentoxifylline addition to thoracic irradiation. A single dose of 14 Gy was given to both lungs with an anterior 4 × 4 cm field at 2 cm depth. Penthoxifylline 3.4 mg/day (equivalent to 1200 mg/day, 70 kg adult dose, calculated according to the mean weight of rats which was 200 gr) orally administered with a feeding tube once daily, including week-ends till the animals were sacrificed. Vitamin E (dl-α-tocopheryl acetate) 1.1 mg/day(equivalent to 400 mg/day, 70 kg adult dose) was injected intraperitoneally (IP) after it dissolved in 0.1 ml olive-oil and continued until the sacrification. Pentoxifylline and vitamin E were started the following day of irradiation. Animals were anesthetized and sacrificed with cervical dislocation, 12 weeks after the irradiation. Both lungs were fixed by tracheal instillation of 10% neutral-buffered formalin, and then embedded in paraffin. Five-micrometer thick sections were stained with Masson's trichrome to visualize fibrosis and collagen. As quantitative end point the extent of radiation-induced fibrosis for each field was graded on a scale from 0 (normal lung) to 8 (total fibrous obliteration of the field). The mean score values were calculated for each group. Kruskal-Wallis One-Way ANOVA method and Bon-ferroni post hock test was used to test the significance of any differences among groups.
Results: The mean value of fibrosis was 6.50 (±058) for Group A, 5.25 (±0.50) for Group B, 2.75 (±0.50) for Group C and 2.25 (±0.50) for Group D. The difference was significant according to Kruskal-Wallis One-Way ANOVA method ($p = 0.004$). When the groups were compared with Bon-ferroni post hock test, the differences between Group A vs Group D ($p < 0.05$) and Group A vs Group C were statistically significant ($p < 0.05$).
Conclusions: This experimental study demonstrates that vitamin E treatment immediately after irradiation protects against radiation-induced pulmonary fibrosis. The combination of vitamin E and pentoxifylline is more effective on modification of the development of pulmonary injury although pentoxifylline itself has limited efficacy which is not stastistically significant.

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Induction of radiation-induced pneumonitis relies on the CD95/CD95-L system

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Pneumonitis constitutes a dose limiting side effect induced by radiotherapy of thorax-associated neoplasms with a lethality up to 10%. However, the molecular mechanisms involved in radiation-induced pneumonitis are not yet understood. Although pneumonitis mostly occurs within irradiated areas of the lung, it may spread to non irradiated areas, indicating that humoral factors may be involved. Complex alterations of cytokine expression pattern in combination with infectious triggers may be of major importance for the induction of pneumonitis.
In this regard, the CD95/CD95-ligand (CD95-L) system has been implicated in proinflammatory cytokine responses. Moreover ionizing radiation induced expression of CD95 and CD95-L. To gain insight into a putative involvement of the CD95/CD95-L system in radiation-induced pneumonitis, mice with a genetically defined deficiency of CD95 receptor (lpr) or CD95-L (gld) and control mice with an intact CD95/CD95-L system (C57BL6/J) were analysed for their susceptibility to develop radiation-induced pneumonitis. After single irradiation of the right hemithorax (0/12.5Gy) of female C57Bl/6J, lpr and gld mice the breathing frequency was determined in a total-body plethysmograph twice weekly for up to 30 weeks. In addition, histopathological alterations judged by alveolar wall thickness, interstitial edema as well as interstitial and peribronchial inflammation were analyzed at days 1, 21, 42, 84 and 210 post-irradiation by using the hematoxylin-eosine staining.
Scoring-criteria for each of the morphologic alterations were as follows: 0:<10%; 1:10–30%; 2:>30–50%; 3:>50–70%; 4 >70% of the fields viewed. A highly significant increase in breathing frequency occurred in irradiated control mice between days 5 and 70. Furthermore, a clear inflammatory response with increased alveolar wall thickness, interstitial edema and enhanced number of inflammatory cells in the interstitial and peribronchial space was observed at days 21, 42 and 84 post irradiation (right lung > left lung). In contrast, no increase in breathing frequency and no inflammatory response were detectable in irradiated gld and lpr mice.
These results suggest that the CD95/CD95 system plays an essential role in the induction of morphological and functional alterations in the lung characteristic for radiation-induced pneumonitis. The identification of the CD95/CD95-L-system may offer new options for prevention or treatment of radiation-induced pneumonitis in the future.