Radiotherapy

Oral presentations (Tue, 1 Nov, 9.15–11.15)
Radiotherapy I

1351 ORAL

Randomised trial of standard 2D radiotherapy (RT) versus 3D intensity modulated radiotherapy (IMRT) in patients prescribed breast radiotherapy

J. Yarnold[1], E. Donovan[2], N. Bleackley[2], S. Reise[2], C. Peckitt[3], S. Patel[3], G. Sharp[1], G. Ross[4], D. Tait[5], P. Evans[2]. [1]*Royal Marsden Hospital, Academic Radiotherapy Department, Sutton, Surrey, United Kingdom;* [2]*Royal Marsden Hospital, Physics Department, Sutton, Surrey, United Kingdom;* [3]*Institute of Cancer Research, Clinical Trials and Statistics Unit, Sutton, Surrey, United Kingdom;* [4]*Royal Marsden Hospital, Breast Unit, Chelsea, London, United Kingdom;* [5]*Royal Marsden Hospital, Breast Unit, Sutton, Surrey, United Kingdom*

Aim: To test standard 2D versus 3D intensity modulated radiotherapy (IMRT) in terms of late changes in breast appearance, discomfort and hardness.
Methods: Between 1997 and 2000, 306 women with larger than average breast size requiring whole breast radiotherapy after breast conservation surgery for early stage cancer were randomised to 2D radiotherapy delivered using standard wedge compensators or to 3D IMRT (test arm). The latter was delivered using physical compensators or a multiple static field technique delivered using a multileaf collimator. The 2D standard wedged plan was calculated on a single transverse contour of the patient through the centre of the breast, accounting for lung. The IMRT compensation was determined from transit dosimetry using electronic portal imaging. Patients were treated with 6 or 10 MV photons. The primary endpoint was change in breast appearance scored from serial photographs taken under standard conditions before radiotherapy and at 1, 2 and 5 years by 3 blinded observers applying a 3-point graded scale (no change, some change, a lot of change). Secondary endpoints included patient self-assessments of breast discomfort, breast hardness, EORTC QLQ C-30/BR-23 and physician assessments of breast induration. Analysis was by intention to treat.
Results: Factors influencing change in breast appearance, including breast size, surgical deficit, axillary surgery, systemic therapies and lymphatic radiotherapy, were well balanced between treatment arms. By 5 years, 44 (14%) patients had died and 9 (3%) had further surgery or reconstruction surgery making assessment impossible. Of the remaining 253 patients, 242 (96%) had clinical assessments, including 237 with photographs. At 5 years, any change (some change or a lot of change) in breast appearance was scored in 73/122 (60%) allocated standard 2D treatment and in 55/115 (48%) patients allocated IMRT ($p = 0.06$). In patients whose maximum dose was >105% or ⩽105% of the prescribed dose, the rates of any change in breast appearance were 71/118 (60%) and 49/107 (46%), respectively ($p = 0.03$). No difference between treatment arms was observed by patients in terms of breast discomfort, hardness or quality of life.
Conclusion: The final analysis strongly suggests that reduction in unwanted radiation dose inhomogeneity in the breast reduces late adverse effects to statistically and clinically significant extents. A beneficial effect on quality of life remains to be demonstrated.

1352 ORAL

Kinetics of response to long-term treatment combining pentoxifylline and tocopherol in patients with superficial radiation-induced fibrosis

S. Delanian[1], R. Porcher[2], J. Rudant[2], J.-L. Lefaix[3]. [1]*Hopital Saint Louis, Radiotherapie, Paris, France;* [2]*Hopital Saint Louis, Biostatistique/ Informatique, Paris, France;* [3]*CEA, DSV/ DRR, Fontenay aux Roses, France*

Background: Radiation-induced fibrosis (RIF), a late damage to normal tissue after radiotherapy (RT), is traditionally considered irreversible. Significant RIF regression has been achieved after treatment combining pentoxifylline (PTX) and tocopherol (vit. E). We focus here on the maximum response, how long it takes to achieve, and changes after treatment discontinuation.
Methods: Among more than 300 treated patients with chronic RT damage, 62 homogenous patients had 74 measurable and symptomatic superficial RIF. RIF analyzed with complete data were assessed in patients treated by RT for breast cancer a mean 7 years previously, in a long (24–48 months) PTX-vit. E (L.PE) group of 37 patients (47 RIF sites) and in a short (6–12 months) PTX-vit. E (S.PE) group of 7 patients (8 RIF sites). Between April 1995 and April 2000, the women were treated with a daily oral combination of PTX (800 mg) and Vit. E (1000 IU). The main endpoint measure was the relative regression of RIF surface area, every 6 months over 5 years, during and after the end of treatment.
Results: Combined PTX-vit. E was continuously effective over several years and resulted in RIF surface area regression (S.PE/ L.PE): −46/−68% at 6 months, −58/−69% at 12 months, −63/−68% at 18 months, −68% at 24 and 36 months. The best representative model of the time-course of regression was found to be of the exponential form $f(t) = a.\exp(-bt) - a$ with t (time from treatment onset), a (maximal surface area regression), and b (kinetics of response). The estimated maximal treatment effect was a mean 68% RIF surface area regression. The time to this effect was a mean 24 months, and was shorter (16 months) in more recent RIF (<6 years since RT) than in longer standing RIF (28 months) ($p = 0.0003$). Symptom severity was halved in both groups: mean SOMA score of −54% at 6 months in S.PE and −47% at 18 months in L.PE. After treatment discontinuation, mean RIF surface area at one year had increased by +40% in S.PE (rebound) and +8.5% in L.PE.
Conclusions: Under combined PTX-vit. E treatment, RIF surface area regression was exponential with a two-thirds maximum response after a mean 2 years. There was a risk of a rebound effect if treatment was too short. Long treatment (⩾3 years) is recommended in severe cases.

References

[1] Delanian et al., JCO. 1999, 17, 3283–90.
[2] Lefaix et al., IJROBP. 1999, 43, 839–47.
[3] Delanian et al., JCO. 2003, 21, 2545–50.

1353 ORAL

Normal tissue protection and modulation of tumor radiation sensitivity by the combination of Pravastatin with radiotherapy

O. Gilliot[1], V. Haydont[1,2], C. Bourgier[1,2], P. Verrelle[4], J. Bourhis[1,3], M. Vozenin-Brotons[1,2]. [1]*IGR/IRSN, UPRES EA 27–10, Villejuif, France;* [2]*IRSN, SRBE/DRPH/LRPat, Fontenay-aux-Roses, France;* [3]*IGR, Radiation Oncology Department, Villejuif, France;* [4]*CJP, Radiation Oncology Department, Clermont-Ferrand, France*

Background: Tumor elimination while minimizing the damage to the surrounding normal tissues is a major goal to improve the therapeutic index of radiation therapy. Recently, R Weichselbaum [1] proposed that "new biological strategies [should] sensitize tumors to radiation and protect normal tissues".
Our laboratory investigates the physiopathological mechanisms of late radiation injury to normal tissue in order to define new therapeutic targets. We recently showed the activation of the Rho pathway in initiation and maintenance of radiation-induced intestinal fibrosis. Furthermore using a pharmacological inhibitor of the Rho pathway, Pravastatin, we have been able to limit radiation-induced fibrogenic differentiation both *in vitro* and *in vivo*, suggesting that Rho inhibition may become a novel anti-fibrotic therapy. Before transfering to the clinical applications, assessment of the effect of [Pravastatin+irradiation] combination on tumor control was required. Therefore, in the present study the effect of Pravastatin+irradiation on tumor radiation response was assessed *in vitro* and *in vivo*.
Material and methods: Modulation of radiation sensitivity was assessed *in vitro* using clonogenic cell survival assay. Cervix carcinoma (HeLa), Colon carcinoma (HT-29) and glioblastoma (SF763) cell lines were subcultured in DMEM complemented with 10% charcoal-stripped FCS and incubated with Pravastatin alone (100–500 &,mu;M), irradiated at 2–6 Gy or treated with combination. Tumor growth delay is currently studied *in vivo*, using HeLa and HT-29 xenograft in nude mice and treated with Pravastatin (30 mg/kg/J), irradiation (2×7.5 Gy) or combination.
Results: Consistent with previous published observations [2], the present *in vitro* experiments showed that Pravastatin exposure alone was able to decrease clonogenic survival at 500 μM (500 μM correspond to Pravastatin ED^{50} *in vitro*). Interestingly, combination of Pravastatin and irradiation more potently decreased clonogenic survival in a dose dependent manner. Additional experiments are currently performed to determine whether the effect is additive or synergistic and the underling molecular mechanisms. Furthermore, the *in vivo* experiments are under analysis.
Conclusion: The present results suggests that the anti fibrogenic agent Pravastatin can sensitize tumor cells to ionising radiation. The molecular mechanism involved are yet undefined, but one attractive hypothesis concerns the inhibition of RhoB, a small GTPase involved in radiation resistance of SF763 and HeLa cells [3]. In addition, combination of Pravastatin with irradiation may allow to achieve a dual objective: simultaneous normal tissue protection and tumor sensitisation.
Acknowledgments: The authors wish to thank Bristol-Myers Squibb for providing Pravastatin

References

[1] Weichselbaum, Nat Med, 2005.

[2] Horigushi et al., Clin Cancer Res, 2004.
[3] Ader et al., Oncogène, 2002; Delmas et al, Int J can, 2002.

1354 ORAL

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

F. Kong[1], J. Hayman[1], R. Ten Haken[1], G. Kelemkerian[2], D. Arenberg[2], S. Lyons[2], A. Turrisi[1], A. Lichter[1], A. Eishbruch[1], T. Lawrence[1].
[1]University of Michigan, Radiation Oncology, Ann Arbor, USA; [2]University of Michigan, Internal Medicine, Ann Arbor, USA

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.

1355 ORAL

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

N.S. Bese[1], F. Munzuroglu[1], B. Uslu[2], S. Arbak[2], G. Yesiladali[3], N. Sut[4], T. Altug[5], A. Ober[1]. *[1]Istanbul University, Cerrahpasa Medical Faculty, Radiation Oncology Department, Istanbul, Turkey; [2]Marmara University, Medical School, Department of Histology and Embryology, Istanbul, Turkey; [3]Cerrahpasa Medical Faculty, Istanbul, Turkey; [4]Cerrahpasa Medical Faculty, Department of Biostatistics, Istanbul, Turkey; [5]Cerrahpasa Medical Faculty, Department of Experimental Animal Breeding and Research, Istanbul, Turkey*

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.

1356 ORAL

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

F. Heinzelmann[1], V. Jendrossek[1], K. Nowak[1], T. Eldh[1], R. Borras[1], R. Handrick[1], W. Budach[2], C. Belka[1]. *[1]University of Tuebingen, Radiation Oncology, Tübingen, Germany; [2]University of Düsseldorf, Radiation Oncology, Düsseldorf, Germany*

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.