Letters to the editor

Randomized phase II trials in lung cancer

In a randomized phase II study, Planting et al. [1], on behalf of the EORTC Lung Cancer Cooperative Group, tested the response rate and morbidity of high-dose split-course radiotherapy *versus* the same radiotherapy preceded by chemotherapy. Comparison of patient characteristics, response, toxicity and survival between the two groups of patients showed no therapeutic benefit for the combined therapy. In their editorial, Sorensen and Hansen [2] reiterate the objectives of randomized phase II trials, as previously described [3]. Numerous biases will be established if the design of clinical trials is defective, especially when the principal aims of studies are not well addressed. The Practical Guide to EORTC Studies [4] published in 1994 says that randomized phase II trials are to be viewed as a simultaneous screening of several compounds and not as comparative trials, adding that the trial may be continued as a randomized phase III trial (...). In such case, however, the protocol should be reviewed, because the aim and endpoints of the phase III trial are not the same as those of a phase II study. It appears that in this study EORTC's recommendations were not followed by its own Lung Cancer Cooperative Group.

As is pointed out in the Editorial [2], we need relevant clinical trials performed by cooperative groups which accrue enough patients for drawing solid conclusions. A comparative study with only a few patients is not very useful. Its results might be added to those of similar trials in comparative tables reviewing a given topic, or perhaps to some other category in future meta-analyses.

A. S. Rubiales & M. L. del Valle
Servicio de Oncología, Hospital Universitario de Valladolid, 47011 Valladolid, Spain

References

1. Planting A, Helle P, Drings P et al. A randomized study of high-dose split-course radiotherapy preceded by high-dose chemotherapy *versus* high-dose radiotherapy only in locally advanced non-small-cell lung cancer. An EORTC Lung Cancer Cooperative Group trial. Ann Oncol 1996; 7(2): 139–44.
2. Sorensen JB, Hansen HH. More power to trials for non-small-cell lung cancer. Ann Oncol 1996; 7(2): 119–20.
3. Simon R, Wittes RE, Ellenberg SS. Randomized phase II clinical trials. Cancer Treat Rep 1985; 69: 1375–81.
4. European Organization for Research and Treatment of Cancer. A Practical Guide to EORTC Studies. Brussels 1994; 64–5.

This letter was referred to the author, who responds as follows:

Colleagues Rubiales and del Valle refer to the EORTC Practical Guide to EORTC Studies dating from 1994. The EORTC guideline indeed reserves the expression randomized phase II trials for simultaneous screening of several compounds and not as a comparative trial.

The study presented in our paper was designed in 1983 and started in 1984 and in those days randomized studies testing the feasibility of two treatment regimens with the option to continue as a phase III study were called randomized phase II studies.

The study presented never continued as a phase III study, and for this reason the protocol never was reviewed with this option as the accrual was too slow. The lesson we learned from this study is that cooperative groups should not run competitive trials. Nevertheless we considered the results of this study to be of interest to be published in spite of the low number of patients.

A. S. T. Planting
Department of Medical Oncology, Rotterdam Cancer Institute, Rotterdam, The Netherlands

Paclitaxel-induced radiation recall dermatitis

Radiation recall dermatitis represents a cutaneous toxicity common to several antitumor antibiotics, particularly adriamycin and dacarbazine. Initially reported by Donalds in 1974 and Greco in 1976, recall dermatitis consists of a cutaneous reaction with erythema, blistering or ulceration occurring geographically in a previous field of irradiation, usually within three to seven days after injection of the antitumor antibiotic [1, 2].

Paclitaxel represents a novel cytotoxic agent with demonstrated activity in different solid tumors, particularly ovarian and breast cancer. Hypersensitivity reactions are among the toxic side-effects of paclitaxel and adequate pretreatment with prophylactic steroids and histamine-antagonists is recommended [3].

We here report the case of a 55-year-old patient with advanced breast cancer developing radiation recall dermatitis after application of paclitaxel. Breast cancer was initially diagnosed in 1993 and the patient underwent radiation therapy of the left breast with 50 Gy after lumpectomy. In December 1994 she developed parasternal and supra- and infraclavicular lymph node metastases which were treated with radiation therapy (54 Gy) to the involved tumor sites with an anterior and posterior radiation field until February 1995. Apart from the history of breast cancer, the patient had no concurrent illness.

While being on tamoxifen therapy in 1995, the patient developed pulmonary and retroperitoneal lymph node metastases and she was treated with six cycles of epirubicin and cyclophosphamide chemotherapy from August to November 1995 resulting in a partial remission. In January 1996 disease progression at pulmonary sites and meningeal involvement with breast cancer was noted. The patient received intrathecal methotrexate combined with cerebral irradiation. Systemic treatment with paclitaxel 175 mg/m^2 as a 3-hour infusion was given in March 1996. Five days after the application

Table 1. Summary of reports of paclitaxel-related radiation recall dermatitis.

Age/sex	Radiation dose	Paxlitaxel dose/ schedule	Interval radiation – paclitaxel	Prior anthracycline therapy	Severity of reaction	Reference
41 female	50.4 Gy	130 mg/m² – 24 h	5–10 days	+ (6 months ago)	Desquamation, necrosis	5
45 female	44 Gy	90 mg/m² – 3 h	7 months	–	Erythema	6
43 female	44 Gy	90 mg/m² – 3 h	6 months	–	Erythema	6
60 female	25 Gy	200 mg/m² – 3 h	4 weeks	–	Erythema, desquamation	7
55 female	54 Gy	175 mg/m² – 3 h	13 months	+ (4 months ago)	Erythema	Current case

of paclitaxel the patient developed supraventricular tachycardia up to 135 beats per minute and erythema of the skin in the formerly irradiated sites of the left chestwall and the back, strictly confined to the previous irradiation fields. No pruritus or blistering or ulceration occurred. The site of cranial irradiation did not show any erythema. Laboratory values on the day of the erythema showed an elevated leukocyte count of 19000/μl and a highly elevated c-reactive protein of 17.9 mg/dl. No specific treatment was initiated and the supraventricular tachycardia disappeared within one day. The erythema completely resolved throughout the next seven days. Reexposition to paclitaxel was not performed.

Paclitaxel has been known as a radiosensitizing agent [4], but recall dermatitis in previous irradiation fields after paclitaxel application has only been reported in four patients before [5–7]. While in the case by Raghavan et al. radiation had stopped only 10 days before the application of paclitaxel, the intervals between radiotherapy and paclitaxel application were between six weeks and six months in the cases reported by Shenkier and Philips. Late occurrence of this reaction may be observed for more than one year after radiation, as demonstrated in our patient (Table 1). Interestingly, neither in our patient nor in the patient reported by Raghavan, previous treatment with anthracycline derivatives had resulted in a radiation recall dermatitis, indicating that different mechanisms may be involved in this type of reaction for paclitaxel and adriamycin. It is also of interest that no radiation recall reaction was observed at the site of the concomitant cranial irradiation in our patient. In summary, radiation recall dermatitis has to be added to the list of possible side effects of paclitaxel treatment. It might be speculated that prophylactic antiallergic medication for the prevention of paclitaxel hypersensitivity may have decreased the occurrence of radiation recall dermatitis and therefore this side-effect has only been observed in a few cases so far.

C. Bokemeyer,[1] C. Lampe,[1] M. Heneka,[2] M. Schabet,[2] M. Bamberg[3] & L. Kanz[1]
[1]*Dept. of Internal Medicine II,* [2]*Dept. of Neurology,* [3]*Dept. of Radiotherapy, Eberhard-Karls-University, 72076 Tübingen, Germany*

References

1. Donaldson SS, Glick JM, Wilbur JR. Adriamycin activating a recall phenomenon after radiation therapy. Ann Intern Med 1974; 81: 407–8.
2. Greco FA, Brereton HD, Kent H et al. Adriamycin and enhanced radiation reaction in normal esophagus and skin. Ann Intern Med 1976; 85: 294–8.
3. Van Herpen CML, Van Hoesel QGCM, Punt CJA. Paclitaxel-induced severe hypersensitivity reaction occurring as a late toxicity. Ann Oncol 1995; 6: 852 (Letter).
4. Tischler RB, Schiff PB, Geard CR et al. Taxol: A novel radiosensitizer. Int J Radiat Oncol Biol Phys 1992; 22: 613–7.
5. Raghavan V, Bloomer W, Merkel D. Taxol and radiation recall dermatitis. Lancet 1993; 341: 1354 (Letter).
6. Shenkier T, Gelmon K. Paclitaxel and radiation-recall dermatitis. J Clin Oncol 1994; 12: 439 (Letter).
7. Phillips KA, Urch M, Bishop JF. Radiation-recall dermatitis in a patient treated with paclitaxel. J Clin Oncol 1995; 13: 305 (Letter).

Clubbing, arthralgia and haemoptysis in a patient with metastatic carcinoma of the breast

Introduction

Clubbing and haemoptysis are recognised features of primary bronchogenic carcinoma and less commonly, secondary lung metastases. We report a case of advanced carcinoma of the breast with lung metastases presenting with clubbing and haemoptysis one year after primary diagnosis.

Case history

A 46-year-old woman underwent wide local excision and axillary dissection followed by adjuvant radiotherapy and tamoxifen for carcinoma of the left breast in May 1994. One year following initial presentation, she was seen with diffuse arthralgia affecting her hands, wrists, ankles and shoulders. She also complained of a dry cough and haemoptysis with flecks of fresh red blood; anorexia, lethargy, night sweats and severe weight loss. On physical examination she was found to be pyrexial (38 °C), cachectic and have marked clubbing of her fingers and toes (Figure 1). Her urea and electrolytes, serum calcium and alkaline phosphatase, erythrocyte sedimentation rate (ESR) and Rh factor were within normal limits. A chest radiograph revealed multiple opacities consistent with pulmonary metastases and radiographs of her extremities were normal. An isotope bone scan was suggestive of bony metastases in the ribs; and a liver ultrasound was normal. Cytology obtained from a CT guided biopsy of a peripheral lung opacity confirmed the presence of malignant cells consistent with metastatic breast carcinoma. These samples were negative on bacterial, fungal and tuberculous culture. In view of the necessity of chemotherapy and the possibility of an infective aetiology for her symptoms, she underwent further investigations. Repeat blood cultures (6 sets),