Pergamon

European Journal of Cancer Vol. 32A, No. 12, pp. 2177–2180, 1996

Printed in Great Britain
0959-8049/96 $15.00 + 0.00

PII: S0959-8049(96)00250-X

Short Communication

Interstitial Pneumopathy After Mantle Field Irradiation for Hodgkin's Disease

H. Pape,[1] A. Mulhern,[1] J.v.d. Haar,[1] I. Ernst,[1] U. Göbel[2] and G. Schmitt[1]

[1]Klinik für Strahlentherapie und Radiologische Onkologie; and [2]Klinik für Pädiatrische Hämatologie und Onkologie, Universität Düsseldorf, Moorenstr.5, 40225 Düsseldorf, Germany

This retrospective analysis was undertaken to determine the incidence of interstitial pneumopathy and the clinical course after mantle field irradiation for Hodgkin's disease focusing on the role of radio- and chemotherapy. 136 patients were evaluable, 40 having received radiotherapy only and 96 patients having received combined radio-chemotherapy. The median follow-up time was 21.5 months. The overall incidence was 19%; 4 patients died of severe interstitial pneumopathy and 3 died of simultaneous severe complications. The radiation dose was correlated with the incidence of interstitial pneumopathy ($P = 0.0021$). Copyright © 1996 Elsevier Science Ltd

Key words: interstitial pneumopathy, mantle field irradiation, Hodgkin's disease, influence of radio- and chemotherapy

Eur J Cancer, Vol. 32A, No. 12, pp. 2177–2180, 1996

INTRODUCTION

BECAUSE OF improved survival and cure rates of Hodgkin's disease, research into treatment-related toxicity is important. Interstitial pneumopathy is a late effect of mantle field irradiation which usually spontaneously subsides, but it can be a very serious clinical event strongly resembling ARDS (Acute Respiratory Distress Syndrome) with lethal outcome. To determine the risk of lung injury after mantle field irradiation for Hodgkin's disease, 136 patients were analysed retrospectively in this study. The endpoints of the study were incidence and clinical course of lung damage and statistical correlation to factors such as age, radiation dose and chemotherapy.

PATIENTS AND METHODS

From 1 November 1979 to 31 March 1992, 151 patients were treated with mantle field irradiation for Hodgkin's disease. 15 patients were lost to follow-up and the remaining 136 were evaluable for this study. Since radiation pneumonitis usually occurs within 6 to 12 months after the start of radiation treatment [21] the follow-up time was restricted to 24 months. The median follow-up period was 21.5 months.

Correspondence to H. Pape.
Received 9 Jun. 1995; revised 15 May 1996; accepted 25 Jun. 1996.

The diagnosis of interstitial pneumopathy was based on patient's history and chest X-ray films monitored during the follow-up period. To assess the incidence of lung injury in this retrospective manner, all radiographic changes including early radiation pneumonitis and late fibrosis were counted as interstitial pneumonitis. *Pneumocystis carinii* in 2 patients and pericarditis in one patient were considered as complications and counted separately.

Severity of pneumonitis was assessed by the following toxicity criteria: grade I (mild), when radiographic changes appeared without clinical symptoms and no need of therapy; grade II (moderate), when radiographic changes were combined with clinical symptoms such of cough and tachypnoe requiring treatment with steroids; and grade III (severe), lethal outcome.

Statistics

Distribution of age, radiation dose and courses of chemotherapy were analysed by descriptive statistical methods. The statistical correlation between the incidence of interstitial pneumopathy and the different factors was determined by the multiple logistic regression analysis [19].

Patients

Of the 136 patients analysed in this study, 71 (52.2%) were male and 65 (47.8%) female with an average age of 31.7 years (9–75 years). Most patients were seen in the

group of 14–30 years (median 28 years). Since age is one of the endpoints, 20 children (< 16 years) were included.

All patients received radiotherapy and have been treated by the mantle field technique including both lungs, partially protected by shielding blocks. Initially, large AP/PA fields were used to include nodal volumes in the mediastinum and the supraclavicular region. After 30.6 Gy or 39.6, depending on the tumour volume, the radiotherapy was limited to the tumour target. The dose was specified to the central axis beam in the middle of the mediastinum. The delivered total dose ranged from 11.7 to 66 Gy. Fraction sizes differed during the period from 5×1.0 Gy to 5×2 Gy with 5×1.8 Gy in 70% of the cases. These mainly homogeneous, conventional fraction sizes made the determination of their value for interstitial pneumopathy impossible. To compare the different treatment schedules, the linear-quadratic model was used. This model describes the relationship between delivered dose and cell damage as a biological effect:

$$\text{BED} = nd\,[1 + d/(\alpha/\beta)].$$

In this equation, BED stands for biological effective dose, n is the number of fractions in a given schedule, d is the dose per fraction and α and β are the linear and quadratic coefficients of the dose response [11]. BED is a measure of the theoretical dose required to produce an isoeffect (E). For reasons of comparison, BED values can be calculated for different fraction sizes in different schedules. Like all biological calculations, this model is not always reliable, since it depends on the repair capacity of different tissues, expressed in the coefficients α and β. The reliability in this calculation is determined by the appropriate α/β ratio. For dose limiting late effects in the lung, a factor of 3 for α/β was chosen [11]. The calculated biological isoeffective doses were referred.

Of the 136 patients, 40 (29%) received radiotherapy only, total mean dose 38.2 Gy (range 19.5–45), mean age 35.3 years (range 9–75); and 96 (71%) received combined radiochemotherapy, total mean dose 37.1 Gy (11.7–66), mean age 30.0 years (11–64). Distribution of age and delivered radiation dose in both groups were comparable.

Children were treated according to the protocol HD-82 (1982–1984) and HD-85 (1985–1986), with two courses of OPPA (oncovin, procarbazine, prednisone and doxorubicin) and 35 Gy involved field radiotherapy (IF-RT). From 1986 to 1989, children were assigned to the HD-87 with two courses of OPPA and 30 Gy IF-RT. Since 1990, the HD-90 protocol was used, which comprises two courses of OPPA for girls and two courses of OEPA for boys (oncovin, etoposide, prednisone and doxorubicin) combined with 25 Gy IF-RT. Adults were not always treated in strict protocols. Patients with advanced disease were given two alternating courses of COPP/ABVD (cyclophosphamide, oncovin, procarbazine, prednisone/doxorubicin, bleomycin, vinblastine and dacarbazine) combined with 40 Gy radiotherapy to the mediastinum, 30 Gy as an extended field (EF) and 10 Gy as an involved field (IF) boost. In case of progression, an alternative approach was adopted, such as IMVP (ifosfamide, methotrexate, etoposide and prednisone) or DEXABEAM (dexamethasone, BCNU, etoposide, Ara-C and melphalan). To assess the role of chemotherapy in interstitial pneumopathy incidence, the overall number of chemotherapy courses were taken into account. On average, 4.8 courses were administered with a median of four and a maximum of 21 courses. Of 96 patients, 86 (89.5%) had been treated with doxorubicin, with an average total dose of 101 mg/m^2 and a maximum total dose of 400 mg/m^3. 75/96 patients (78.1%) had been treated with bleomycin. The average total dose was 38.4 mg/mg^2 and the maximum total dose was 200 mg/m^2.

RESULTS

Of the 136 patients included in the analyses, 26 (19%) developed interstitial pneumopathy. 6 out of these 26 cases had received radiotherapy (mean dose 41 Gy) only, and the average age was 56.2 years. 20 patients (21%) developed interstitial pneumopathy after combined radiochemotherapy. They were younger than the aforementioned group (average 28.8 years) and received, on average, nine courses of chemotherapy (Table 1). Of the 26 cases of interstitial pneumopathy, 13 were grade I, 6 grade II and 4 grade III with lethal outcome. 3 had simultaneous fatal complications. Details of the 7 patients who died are shown in Table 2, indicating a short latency period and a hyperacute course of illness. 2 elderly patients died of simultaneous *pneumocystis carinii* infection.

Multiple logistic regression analysis (SPSS) of the whole group of 136 patients showed that only radiation dose ($P = 0.0044$), number of chemotherapy courses ($P = 0.0031$), age ($P = 0.0264$), and cumulative doxorubicin dose ($P = 0.0288$) were significant factors. In a second analysis, focused on the 96 patients who received combined radiochemotherapy, the only factor that was significant was the radiation dosage ($P = 0.0021$). Chemotherapy achieved marginal significance ($P = 0.0508$). However, given the limited cohort on which the investigation was based, the results obtained must be interpreted with some caution.

DISCUSSION

Early studies from Gilbert and Peters laid the basics for modern treatment of Hodgkin's disease and demonstrated that radiotherapy was able to cure this condition [9, 18]. It was the Stanford group led by Kaplan [11–13] that systematically studied the role of radiotherapy. With the introduction of chemotherapy, the role of radiotherapy in Hodgkin's disease changed drastically. Cure was achieved even in advanced stages and patterns of side-effects altered. The clinical course of interstitial pneumopathy had to be re-analysed in this combined setting.

Reports on the incidence of treatment-related interstitial pneumopathy in Hodgkin's disease vary from 6 to 85% [4, 21]. Reasons for this broad divergence might be related to different evaluation criteria in the area of image analysis and to the quality of different follow-up schedules. Slanina and coworkers delivered 46 Gy to the mediastinum and followed the patients regularly in short time intervals. They reported an 88% incidence for both acute pneumonitis and late fibrosis and 44% of the patients remained subclinical [21]. Castrup and associates found a 16.7% rate of acute pneumonitis and 5.8% of late fibrosis after 40 to 45 Gy delivered to the mediastinum [4]. Müller and coworkers observed 37% acute interstitial pneumopathies and 33% fibroses following radiotherapy of lung cancer with 60 to 70 Gy. These

Table 1. Treatment characteristics of 20 patients with interstitial pneumopathy after combined radiochemotherapy

Patient	Age (years)	Radiation dose (Gy)	Number of CHT courses	Cumulative dose of doxorubicin (mg/m^2)	Cumulative dose of bleomycin (mg/m^2)
1	25	57.6	8	150	60
2	20	44.0	4	50	20
3	36	39.6	9	150	60
4	23	45.0	8	200	80
5	42	32.6	6	—	—
6	16	40.0	5	130	20 + BMT
7	28	39.6	8	100	40
8	26	50.4	4	100	40
9	17	39.6	8	200	80
10	31	54.2	8	200	80
11	20	44.0	4	—	—
12	46	30.6	8	200	80
13	24	39.6	4	100	40
14	62	36.0	6	150	60
15	27	64.0	10	150	120
16	18	36.5	21	300	120
17	28	50.4	16	350	140
18	11	66.0	17	350	200
19	23	39.6	16	150	60
20	53	30.6	8	200	80
	Mean 28.8	Mean 44	Mean 8.9	Mean 161.5	Mean 66

Gy, Gray; BMT, bone marrow transplantation; CHT, chemotherapy.

patients received combined chemotherapy with cisplatinum and etoposide [17]. We found an incidence of 19% with an average radiation dose of 37 Gy.

Notwithstanding intensive research, the pathogenesis and aetiology of interstitial pneumopathy still remains unclear. Research today concentrates on: vascular and immunological reactions [1, 2, 5] of type II pneumocytes [1] and on alterations in extracellular matrix and growth factor-induced collagen production [7]. Most clinical reports can be found in the field of bone marrow transplantation. Unfortunately, high dose radio- and chemotherapy is being used with a very complex field of risk factors in a multifactorial background. This means that the role of any one factor cannot be reliably discriminated.

Risk factors, such as age [15] concomitant infection, emphysema or obstructive disease, may be cofactors. In contrast to patients with lung cancer most of our patients were young (on average 31 years) and had healthier normal lung tissues. Pretherapeutic emphysema or obstructive lung disease were not observed.

Kaplan and coworkers systematically studied treatment-related side-effects. Their basic studies on the underlying principles of radiation-induced pneumopathy determined the appropriate dose and fraction size and how to spare volume to minimise normal tissue complications [12–14]. From these early studies, it was discovered that interstitial pneumopathy increases with increased radiation dosages. Our results corroborate these early investigations. Fractionated application of the total radiation dose is the common way by which sparing of normal tissue is achieved in clinical radiotherapy [16]. Both pneumonitis and fibrosis could be reduced when the size of the dose per fraction was reduced [16]. Castrup and Slanina observed that fraction size and type of fractionation had only minor influence on interstitial pneumopathy [4, 21] with conventional fractionation. In our cohort, most of the patients had homogeneous conventional fraction sizes of 1.8 Gy.

Treatment volume is an important factor, and it has been shown that clinical symptoms are rare if radiation is restricted to a volume of 20% [16]. However, in our study, the irradiated volume could not be defined and, therefore, its effect could not be examined.

Although rare, severe pneumonitis has been reported after combined chemo- and radiotherapy [6, 10]. Fryer and co-

Table 2. Clinical course and latency period of patients with lethal outcome

Patient	Age (years)	Radiation dose (Gy)	Number of CHT courses	Latency period	Cause of death
1	53	30.6	8	3 months	*Pneumocystis carinii*
2	62	36.0	6	3 months	*Pneumocystis carinii*
3	20	45.0	4	6 weeks	Pericarditis
4	16	40.0	5 + BMT	4 days after BMT	Acute interstitial pneumonia
5	70	40.0	—	4 weeks	Pneumonia; fibrosis at autopsy
6	67	45.0	—	Subsequent	Interstitial pneumonia, deceased after 15 weeks
7	27	64.0	10	3 weeks	Acute interstitial pneumonia

BMT, bone marrow transplantation; CHT, chemotherapy.

workers described 9% subacute grade 3 or 4 pulmonary toxicity in 64 children after 12 cycles of ABVD plus low-dose radiotherapy with only 5% being symptomatic [8]. The EORTC H6F and H6U trial observed a cumulative incidence of respiratory complications of 12.5%, which usually became symptomatic 6 to 12 weeks after irradiation. Two or more years after radiotherapy, a reduced vital capacity (VC) was more frequently observed in patients treated with ABVD than with MOPP (12% versus 2%; [3]). In general, pulmonary toxicity was scored more severe in ABVD- than in MOPP-treated patients [22]. Comparing MOPP or ABVD in combination with radiotherapy, Santoro and associates observed three fatal cases with interstitial pneumonitis in each arm. They failed to demonstrate any difference [20]. In our inhomogeneous group we saw that the amount of chemotherapy has a marginal influence on the incidence of pneumonitis ($P = 0.0508$). The main factor was radiation dose ($P = 0.0021$). Patient age [15] as well as cumulative adriamycin and bleomycin dose seem to have some impact but did not achieve statistical significance in this study, probably due to the small numbers and the retrospective setting of this trial.

1. Adamson IYR, Bowden DH. The type 2 cell as progenitor of alveolar epithelium regeneration. *Lab Invest* 1974, **30**, 35–42.
2. Adamson IYR, Bowden DH. Endothelial injury and repair in irradiation induced pulmonary fibrosis. *Am J Pathol* 1983, **112**, 224–230.
3. Carde P, Hagenbeek A, Hayat M, *et al.* Clinical staging versus laparotomy and combined modality with MOPP versus ABVD in early stage Hodgkin's Disease: Th H6 twin randomized trials from the European Organization for Research and Treatment of Cancer Lymphoma Cooperative Group. *J Clin Oncol* 1993, **11**, 2258–2272.
4. Castrup W, Wannemacher M, Blömer M, *et al.* Strahlenpneumonitis und Strahlenfibrose nach systematischer Bestrahlung der Lymphknoten-regionen des Thorax bei der Lymphogranulomatose. *Strahlentherapie* 1976, **152**, 15–21.
5. Cogle JE, Lambert BE, Moore SR. Radiation effects in the lung. *Environ Health Perspect* 1986, **70**, 261–291.
6. McEvans TW, Anulty RJ, Rogers DF, Fan Chung K, Barnes PJ, Laurent GJ. Bleomycin–induced lung injury in the rat. Effects of the platelet-activating factor (PAF) receptor antagonist BN 520211 and platelet depletion. *Environ Health Perspect* 1990, **85**, 65–69.
7. Finkelstein JN, Johnston CJ, Baggs R, Rubin P. Early alterations in extracellular matrix and transforming growth factor beta gene expression in mouse lung indicative of late radiation fibrosis. *Int J Radiat Oncol Biol Phys* 1994, **28**, 612–631.
8. Fryer CJ, Hutchinson RJ, Krailo M, *et al.* Efficacy and toxicity of 12 courses of ABVD chemotherapy followed by low dose regional radiation in advanced Hodgkin's disease in children: a report from the Children's Cancer Study Group. *J Clin Oncol* 1980, **8**, 1971–1980.
9. Gilbert R. Radiotherapy in Hodgkin's disease (malignant granulomatosis) anatomic and clinical foundations: governing principles: results. *Am J Roentgenol* 1939, **41**, 198–241.
10. Gros NJ. Pulmonary effects of radiation therapy. *Ann Intern Med* 1977b, **86**, 81–92.
11. Joiner MC. The linear–quadratic approach to fraction. In G. Gordon Steel, ed. Basic Clinical Radiobiology. London, Edward Arnold Publishers, 1993, 55–64.
12. Kaplan HS. Evidence for a tumoricidal dose level in the radiotherapy of Hodgkin's disease. *Cancer Res* 1966, **26**, 1221–1224.
13. Kaplan HS, Stewart JR. Complications of intensive megavoltage radiotherapy for Hodgkin's disease. *Natl Cancer Inst Monogr* 1973, **36**, 439–444.
14. Kaplan HS. Hodgkin's disease, 2nd edn. Cambridge, Massachusetts, Harvard University Press, 1980, 366–441.
15. Kola K, Kusumoto S, Watanabe K, Nishikawa K, Harada K, Ebihara H. Age factors relevant to the development of radiation pneumonitis in radiotherapy of lung cancer. *Int J Radiat Oncol Biol Phys* 1988, **14**, 367–371.
16. Molls M, van Beuningen D. Radiation injury of the lung: experimental studies, observation after radiotherapy and total body irradiation prior to bone marrow transplantation. In Scheerer E, Streffer Ch, Trott R, eds. *Radiopathology of Organs and Tissues.* Heidelberg, Springer Verlag, 1991, 369–404.
17. Müller G, Kiricuta IC, Stieß J, Bohndorf W. Strahlenpneumonitis und Lungenfibrose nach CT—geplanter Radiotherapie des Bronchial-karzinoms. *Strahlenther Onkologie* 1994, **170**, 400–407.
18. Peters MV. A study of survival in Hodgkin's disease treated radiologically. *Am J Roentgenol* 1950, **63**, 299–311.
19. Sachs L. Partielle und multiple Korrelationen und Regressionen in: Angewandte Statistik: Anwendung statistischer Methoden. Heidelberg, Springer-Verlag, 1992, 570–577.
20. Santoro A, Bonnadonna B, Valagussa P, *et al.* Long term results of combined chemotherapy–radiotherapy approach in Hodgkin's disease: superiority of ABVD plus radiotherapy versus MOPP plus radiotherapy. *J Clin Oncol* 1987, **5**, 27–37.
21. Slanina S, Wannemacher M, Bruggmoser G, Krüger H-U. Die pulmonale Strahlenreaktion im Röntgenbild. Intensität und Häufigkeit röntgenmorphologischer Veränderungen der Lunge und des Mediastinums nach Mantelfeldbestrahlungen mit 4 MeV-Photonen und Satellitentechnik. *Radiologie* 1982, **22**, 74–82.
22. Zucali R, Pagnoni AM, Zanini M, *et al.* Radiological and spirometric evaluation of mediastinal and pulmonary late effects after radiotherapy and chemotherapy for Hodgkin's disease. *J Eur Radiother* 1981, **2**, 169–178.