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Acknowledgements—We thank the Finnish National Mesothelioma Pathology Panel (Eero Taskinen, Sisko Anttila and Tauno Ekfors) and the EORTC Lung Cancer Cooperation Group Mesothelioma Pathology Panel (Dr H. Planteydt) for classifying the tumours and Anne Hand for linguistic revision. Supported by the Finnish Cancer Society.

Eur J Cancer, Vol. 28A, No. 8/9, pp. 1379–1380, 1992.
Printed in Great Britain

0964–1947/92 $5.00 + 0.00
Pergamon Press Ltd

Reducing the Toxicity of the Combined Modality Therapy of Favourable Stage Hodgkin's Disease

Saul A. Rosenberg

INTRODUCTION

FAVORABLE STAGE or limited extent Hodgkin's disease is highly curable. Depending on the age of the patient, if combined modality therapy (both radiation and chemotherapy) is employed, 90% or more of patients can be cured of the disease. Even with less favourable settings, combined modality therapy can eliminate the disease in approximately 75% of patients. Achievement of these excellent results, however, requires the use of detailed diagnostic or staging methods and maximal treatment programs. These methods are associated with considerable acute toxicity and morbidity and serious long-term morbidity and mortality. The succcessful treatment of patients with Hodgkin's disease 20 or more years ago has allowed us to recognise and quantify the serious and sometimes fatal treatment complications. The challenge that faces the clinical investigator of Hodgkin's disease today, is to reduce or eliminate the most serious acute and late management toxicities, without sacrificing the excellent curative treatment results which are now possible.

The major problems

The most serious acute and long-term toxicities for patients with favorable stage Hodgkin's disease that might be reduced or avoided are (*potentially fatal) staging exploratory laparotomy*, the asplenic state, surgical or radiation induced*, the severe and repetitive nausea and vomiting of chemotherapy, radiation induced abnormalities of bone and muscle growth and development, radiation pneumonitis and carditis*, chemotherapy and/or radiation induced sterility, chemotherapy induced secondary acute leukemia*, radiation induced secondary cancers*, radiation induced coronary artery disease*, prolonged treatment programs (6 months or longer).

Combined modality therapy

The use of both radiation and chemotherapy for the primary management of patients with Hodgkin's disease is controversial. Very few properly randomised studies can demonstrate a long term survival advantage resulting from the use of both modalities in primary management. This is because patients who are carefully staged and treated with radiation alone can be successfully treated with combination chemotherapy if they develop relapse of their disease. Slight survival advantages of combined modality therapy are diminished or erased by treatment-related deaths, more frequent after utilising maximal combined modality therapy [1].

This is not the situation for children, however, and lessons in treating adults can be learned from the treatment results and protocols for treating children. Because of the bone and growth development abnormalities of full dose irradiation of children, reduced radiation doses and fields are employed, and combination chemotherapy is always used. In some centers, staging laparotomy with splenectomy is avoided because adequate chemotherapy for occult disease is routinely utilized. At Stanford, children are currently clinically staged and treated with combination chemotherapy, with reduced cumulative doses of the major toxic drugs [three cycles of mustine, vincristine, procarbazine and prednisolone (MOPP) and three cycles of ABVD] to minimise the long-term risks of secondary AML, sterility and late cardiopulmonary toxicity of ABVD. The results have been excellent [2].

The Stanford approach for adults has been different. A relatively mild combination chemotherapy regimen has been devised, VBM (vinblastine, bleomycin and methotrexate) and used in combination with limited irradiation fields [3]. The VBM is well tolerated, acutely, with very little nausea, vomiting or hair loss, does not induce male or female sterility, and theoretically, should not induce secondary leukemia. The success of this management approach for laparotomy staged patients has lead to its evaluation for clinically staged patients. The results, to date, are very early but also encouraging. It would appear that maximal chemotherapy programs, associated with severe acute toxicity, sterility, secondary acute leukemia, and cardiomyopathy are not necessary to control minimal or occult Hodgkin's disease.

The goal of reducing long term serious morbidity is also appropriate for patients with more advanced and unfavourable Hodgkin's disease. A 12-week, dose-intensive regimen (Stanford

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This paper was presented at an international symposium on Hodgkin's disease, Royal Marsden Hospital, London, on 15–16 April 1991.
Received 22 Nov. 1991; accepted 17 Mar. 1992.

V) is being tested. Patients receive chemotherapy weekly, with myelo suppressive drugs at full dosage bi-weekly. By utilizing seven active agents, the cumulative dose of alkylating agents is only 25% of the amount in MOPP, the adriamycin is only 50% and the bleomycin is only 25% of the amounts in ABVD. No procarbazine or dacarbazine are given. Patients with initial bulky disease, or who have residual abnormalities receive adjuvant radiotherapy, to limited fields in the amount of 35 Gy. To date, 23 consecutive patients have achieved a complete remission of very unfavourable disease. Fertility appears to be preserved. Secondary neoplasms and late cardiac complications should be reduced.

CONCLUSION

It may well be that the preferred therapy of Hodgkin's disease in the future will utilise combined modality programs, to avoid staging laparotomy with splenectomy and reduced cumulative doses of both irradiation and the most toxic chemotherapeutic agents. These changes in management, however, should be developed and evaluated step-wise and gradually, since curability and comparisons of toxicities will require 5 to 10 years of careful documentation.

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Eur J Cancer, Vol. 28A, No. 8/9, pp. 1380–1386, 1992.
Printed in Great Britain

0964–1947/92 $5.00 + 0.00
Pergamon Press Ltd

Curative Non-surgical Combined Treatment of Squamous Cell Carcinoma of the Oesophagus

Thierry Zenone, Pascale Romestaing, René Lambert and Jean-Pierre Gerard

Between April 1982 and June 1989, 65 patients (15 T1, 13 T2, 32 T3, 5 T4) with squamous cell carcinoma of the oesophagus were treated with a curative intent with multimodality combined treatment. A first course of 5-fluorouracil and cisplatin was given during work up, especially if NdYAG laser therapy was used. Irradiation was started 3–4 weeks after induction and two courses of concomitant chemotherapy were given during the radio therapy (aiming at 64 Gy over 7 weeks). Actuarial survival was 79.6% at 1, 36.7% at 3 and 26.7% at 5 years. 5 year survival rates were 56.3% for T1, 29.8% for T2 and 12.9% for T3. All T4 cases died within 16 months. Complete initial disease response was achieved in 76%. Tolerance was good. Thus patients with squamous cell carcinoma of the oesophagus can have long survival and may be cured with combined modality therapy. This treatment may be an alternative to radical surgery when there is a high risk of operative mortality.
Eur J Cancer, Vol. 28A, No. 8/9, pp. 1380–1386, 1992.

INTRODUCTION

THE PROGNOSIS for a patient with oesophageal carcinoma is poor due to frequent occurrence of both distant metastasis and local recurrence. A major review of reported surgical and radiotherapeutic studies in 1980 revealed an average 5 year survival of 4–6% [1, 2]. Due to advances in technology, improvements in anaesthesia, decrease in postoperative mortality and morbidity rates, the survival has improved during the past decade and surgery is usually considered as the main curative treatment of this cancer. With radical oesophagectomy, between 10 and 30% of patients survive at 5 years [3–6]. Adjuvant therapy to surgery has been used to try and improve these results. Four randomised trials [7–10] have evaluated the effect of preoperative radiotherapy and showed no significant survival improvement in the irradiated group. Another prospective randomised trial [11] has evaluated postoperative radiotherapy and achieved similar results.

When patients are ineligible for surgery, combined modality treatment can be used sometimes in a curative intent [12, 13]. Renewed interest in this problem was stimulated by the encouraging results reported earlier [14–16] when 5-fluorouracil (5-FU) infusion and mitomycin has been combined with concurrent irradiation. Cisplatin may replace mitomycin because of the myelotoxicity of the latter and high response rate of cisplatin on epidermoid carcinoma. 5-Fluorouracil and cisplatin can be considered as radiosensitisers in humans [17]. The Wayne State University experience [18, 19] gave very encouraging results

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Presented at the Third International Congress on neoadjuvant chemotherapy, Paris, France, February 1991.
Revised 17 Feb. 1992; accepted 20 Feb. 1992.