Complications in the treatment of Hodgkin's disease

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Summary

Early Hodgkin's disease is curable with radiotherapy, while combination chemotherapy is curative for stages III and IV. The acute side-effects of treatment (haematological, infectious and neurological toxicity), as well as the late side-effects (sterility, cardiac and pulmonary damage and secondary neoplasms), are therefore of major concern. Data on 60 patients treated over a 12-year period in Bloemfontein were analysed. The acute and chronic complications encountered were in the range expected and 6 patients developed secondary neoplasms. The possible reduction of these complications is discussed. It is concluded that the oncologist should select the best treatment consistent with a good chance of a durable remission but must weigh this against not only short-term but also long-term toxicity.

Major achievements in the treatment of Hodgkin's disease (HD) have been the introduction of extended-field intensive radiotherapy with a high cure rate for early-stage HD1 and combination chemotherapy for stages III and IV disease.2 A large number of patients (more than 60%) will survive free of disease for 10 years or more but may suffer from the complications of treatment.3 Radiotherapy can result in bone-marrow toxicity, cardiac and lung damage, endocrine and neurological dysfunction.4,5 Effective chemotherapy will also result in bone-marrow depression and neurological and gastro-intestinal toxicity.7 Gonadal dysfunction may follow.8 Combined modality treatment enhances these complications and leads to an increased incidence of secondary neoplasms.9,10 In a population of young patients this is of major concern.

This study examines the complications of treatment and possible ways to avoid them are discussed. Of special interest is the effect of treatment on pregnancy.11 An individual treatment policy for every patient, carefully avoiding inadequate treatment, is mandatory.

Patients and methods

From 1970 to 1982, 60 previously untreated patients who had a histological diagnosis of HD and could be evaluated, were seen at National Hospital, Bloemfontein. The median age was 43 years, and there were 23 females and 37 males. The median follow-up period was 7 years. Twelve patients had stage I disease, 19 stage II, 20 stage III and 9 stage IV. Radiotherapy alone as initial treatment was given to 24 patients, and of these 7 had subsequent chemotherapy (administered in the same dosage as for patients on initial chemotherapy) for relapse. Thirty patients had chemotherapy as initial treatment and of these 3 had subsequent radiotherapy (3000 cGy in 2 weeks, 10 daily fractions of 300 cGy; in 2 patients the heart was included in the portals) for relapse. Three patients were treated with combination therapy consisting of the concurrent administration of radiotherapy (total nodal irradiation (TNI) or extended mantle (EM)) and low-dose oral cyclophosphamide chemotherapy (Table I).

Radiotherapy was given with an 8 MeV linear accelerator using either total nodal irradiation (TNI) (12 patients) or an extended mantle (EM) (12 patients). Fractions of 300 cGy were given 3 times a week to the upper half of the body for 6 doses, then the lower body was treated in similar fashion. After this the upper and lower halves of the body were again treated with 7 fractions each. Of the 24 patients 9 had stage I and 15 stage II disease.

Cyclophosphamide, vincristine, prednisone and procarbazine (COPP) was given to 15 patients, 9 patients received nitrogen mustard, vincristine, prednisone and procarbazine (MOPP) and 6 received nitrogen mustard, vinblastine, prednisone and procarbazine (MVPP). Standard dosages were used and patients received a minimum of 6 cycles every 4 weeks. If remission was achieved in this period the cycles were lengthened to 7-week intervals for 4 cycles and then 12-week intervals for 4 cycles. Patients had to be in remission for at least 2 cycles before time intensity was reduced. The total duration of treatment was 2 years. The percentages of planned dose of chemotherapy given for MOPP was 91%, COPP 86% and MVPP 91%.

Results

Radiotherapy

The acute complications are shown in Table II. Two patients in the TNI group died of the complications of bone-marrow depression. Chronic complications included chronic dry mouth (2 patients), proven constrictive pericarditis (1 patient) and restrictive lung disease (1 patient).

Chemotherapy

The acute complications are shown in Table III. Two patients died from haematological complications and 2 from infectious complications. Late side-effects included infertility in 4 male patients (confirmed on sperm count to be azoospermic). One patient died from HD relapse and autopsy showed necrosis of both testes. Three women complained of infertility and proved constrictive pericarditis (1 patient) and restrictive lung disease (1 patient).

Radiotherapy followed by chemotherapy for relapse

Two of these patients developed severe (1 life-threatening and 1 lethal) bone-marrow toxicity. A further patient died of infectious complications.
Chemotherapy with radiotherapy for persistent disease

Both patients in whom the heart was included in the portals, developed acute pericarditis. One of the 3 patients in this group developed life-threatening and 1 lethal bone-marrow toxicity.

Initial treatment with radiotherapy and chemotherapy

The 3 patients developed surprisingly little toxicity but the oral cyclophosphamide dosage was probably suboptimal.

Secondary neoplasms

Six patients (10%) developed secondary neoplasms (Table IV). One patient treated with radiotherapy developed an immunoblastic lymphoma. Among the patients treated with chemotherapy 1 developed lymphocytic lymphoma, 1 acute non-lymphocytic leukaemia (ANLL) and 1 hypernephroma. One patient treated with both modalities developed a myelodysplastic syndrome leading to ANLL and 1 a malignant melanoma.

Complications of treatment during pregnancy

One patient with stage IIA disease was 28 weeks pregnant and treatment was postponed for 6 weeks to allow the fetus to mature. During this period the mediastinal mass became untreatable by radiotherapy and so, after the delivery of a normal baby, she was given chemotherapy with a good result. However, this patient fell pregnant again while on combination chemotherapy and the pregnancy was terminated at 22 weeks. A further patient with stage...
III A disease also became pregnant and, because she was on combination chemotherapy, this was terminated.

Discussion

Complications of radiotherapy

The volume, time, dose relationship and technique of radiotherapy are important factors in determining the complications of radiotherapy. Good technique with a linear accelerator is mandatory. Doses from a minimum of 4000 - 4400 cGy in 4 - 4½ weeks are adequate for tumour masses and there is evidence suggesting that 3600 cGy is adequate for subclinical disease. 4

In our series patients treated with TNI developed more life-threatening and lethal bone-marrow toxicity than patients treated with EM. The incidence of severe bone-marrow toxicity was higher than expected in TNI patients. The use of large fractions results in a greater radiobiological effect. If 3 fractions of 300 cGy per week are compared with the conventional 5 fractions of 200 cGy per week, the larger fraction regimen at the same total dose level produces a greater radiobiological effect, especially when a large volume of bone marrow is treated. The use of TNI can be avoided in the majority of patients without compromising survival. 5 Approximately 38% of active bone marrow is found in the sacrum and pelvis resulting in more bone marrow irradiated with TNI as opposed to lesser fields. Involved field radiation in children will give less growth retardation and other late organ effects if the radiotherapist is prepared to accept a somewhat higher recurrence rate, which nevertheless leaves patients treatable with chemotherapy.

One patient treated with radiotherapy initially developed constrictive pericarditis. This low incidence was related to the use of opposing fields, limiting the number of hearts included in the portals and careful consideration of the dose given.

The incidence of radiation pneumonitis (1 patient) was also low because shrinking field techniques were used with careful consideration of the dose.

There were no cases of proven hypothyroidism. However, a careful search for this complication is necessary in every patient. No neurological complications were observed — careful attention was given to avoiding both overlap of any radiation portals and exceeding spinal cord tolerance.

Complications of chemotherapy

Haematological, gastro-intestinal and neurological toxicity was within the expected range, 6 with 7 of 33 patients developing major bone-marrow toxicity. However, 7 patients developed major infections, which is more than expected, and 2 patients developed major neurological complications.

Carmustine, cyclophosphamide, vincristine, procarbazine and prednisone (BCVPP) was tested in a prospective randomised trial by the Eastern Cooperative Oncology Group and found to have significantly less toxicity with longer complete remission and greater survival. 7 However, the addition of carbustine to MOPP may lead to an increase in secondary neoplasms.

Approximately 90% of men and 40% of women treated with MOPP will have major gonadal dysfunction. 8 Sterility was a documented problem in 7 patients in this series. Doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) produces less problems with gonadal dysfunction but longer follow-up is necessary. 8 ABVD is a good and apparently non-cross-resistant alternative to MOPP, but the results of a trial by the Cancer and Acute Leukemia Group B is still awaited before the efficacy of this treatment is confirmed as an alternative front-line regimen.

Complications of combined modality treatment

In this series the second modality was used mainly as salvage treatment, which resulted in a high incidence of complications especially radiation-induced pericarditis and haematological depression. The use of 300 cGy fractions in a schedule of 5 fractions per week for 2 weeks in these patients resulted in a greater radiobiological effect than would be expected from using conventional fractions of 200 cGy to the same dose level. In patients with extensive earlier chemotherapy exposure the larger fractions may have accounted for the increased incidence of radiation pericarditis.

Combined modality treatment is mostly indicated for patients with massive mediastinal disease who are at high risk for relapse with radiotherapy alone. The increased toxicity and increased incidence of secondary neoplasms restricts the use of combined modalities as initial treatment to the setting of a clinical trial.

HD and pregnancy

This occurred in 2 patients and necessitated a change in the treatment plan and therapeutic abortion. Adequate birth control is vital in patients on chemotherapy in their reproductive years. Careful consideration of the effect of chemotherapy and radiotherapy on the fetus in the specific trimester is needed and each patient should be treated according to her individual needs. It is essential that a patient is not given inadequate treatment because she is pregnant. 9

Secondary neoplasms

In this series 10% of patients developed secondary neoplasms. This — especially ANLL — represents one of the most important long-term complications of combined modalities. Bonadonna et al. 9 cite four major series (National Cancer Institute, Stanford, Southwest Oncology Group, and Milan) showing that radiotherapy alone rarely causes this complication (0.0 - 0.6%).

In the larger series, chemotherapy with alkylating agents and procarbazine creates a 1.4 - 6% actuarial risk of patients developing ANLL. A combination of radiotherapy and chemotherapy as initial treatment results in an ANLL incidence of 2.4 - 7.2%, but intensive radiotherapy followed by intensive chemotherapy for relapse may cause an even higher incidence (7.5 - 15.5%). None of the patients treated with ABVD plus radiotherapy in Milan (median follow-up 8 years) developed ANLL. 9 However, in a report by Amondari et al. 10 1 patient treated with radiotherapy and ABVD developed ANLL and so the leukaemogenic potential of ABVD remains uncertain. Patients are also at risk of developing non-Hodgkin's lymphomas and other soft-tissue tumours.

Conclusion

Hodgkin's disease is potentially curable. With a powerful armamentarium of therapeutic modalities at his disposal the oncologist must select the treatment that will ensure a maximum chance of a cure. However, he should be aware of the complications of any treatment and strive to reduce them to a minimum.

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Variations in mortality of the coloured, white and Asian population groups in the RSA, 1978-1982

Part I. All causes


Summary

Previous reports, based largely on the 1970 census and the 8th revision of the International Classification of Diseases, (ICD-8) have suggested that marked differences in mortality exist between population groups in the RSA. In this article the ICD-9 classification of causes of death and 1980 census are used to assess whether the trends have continued through to the present time. Total mortality data in the RSA for whites, coloureds and Asians for the 5-year period 1978-1982 are presented. The 1980 national census provided the denominator population data. Annual age- and sex-specific mortality rates were higher for coloureds than for whites or Asians, the differences being most marked in childhood. There appears to have been little change in total standardised mortality rates among whites over the 5-year period, while increases have occurred among coloureds of both sexes and among Asian males. Analysis of proportional mortality stresses the relatively large proportion of deaths accounted for by external causes and infections among coloureds and by cardiovascular diseases among whites and Asians. There is an urgent need for the health services to take note of these data in order to provide for the varied needs of the population.

The RSA is genetically, culturally and socially a heterogeneous society, each section of the population having a distinctive disease profile. Despite inaccuracies in diagnosis and registration and other inherent sources of bias, national mortality statistics are at present an acceptable way of tapping this rich source of epidemiological data. 6 A number of publications based on the previous International Classification of Diseases (8th revision) (ICD-8) and the 1970 census, and in some instances focusing on specific age groups, have suggested that there are major differences in mortality between the population groups.7,8 The aim of this and the subsequent articles in the series is to explore differences and chronological fluctuations in mortality between whites, coloureds and Asians, using the updated census and ICD-9 criteria to assess whether the trends previously suggested have continued through to the present time. This article deals with total mortality; the subse-