Review

Long-term toxicity of the treatment of Hodgkin's disease

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Summary

At the present time, the majority of patients who develop Hodgkin's disease can be cured with radiotherapy and/or chemotherapy. A long follow up of cured patients has shown that the cumulative toxicity from treatment related complications rivals the mortality from Hodgkin's disease. In addition to late fatal complications, delayed adverse effects of therapy on the thyroid, reproductive system, and bones are burdens many patients have to bear. Future treatment regimens for Hodgkin's disease will be designed attempting to minimize these complications. Follow up of those patients now in remission should focus on the prevention of morbidity and mortality by anticipating and preventing late complications.

Key words: Hodgkin's disease, late toxicity, treatment

Introduction

Few cancers treated with radiotherapy and/or chemotherapy have as high a cure rate as is found in Hodgkin's disease. Contributions of many clinical investigators have led to the cure of localized and regional Hodgkin's disease with radiation. More recently, the use of combinations of active chemotherapeutic agents has allowed the cure of patients with widespread Hodgkin's disease. Today all patients at diagnosis have a chance for long term disease free survival and this goal is realized at approximately 75% of patients.

It has become apparent that a significant cause of death in patients treated for Hodgkin's disease is related to complications of therapy rather than the cancer itself [1, 2]. The combination of excess mortality from cancer or from treatment related complications makes patients treated for Hodgkin's disease die more frequently than matched controls over 20 years of follow-up [1, 2]. By 15 years of follow-up, the majority of deaths are related to treatment related complications while deaths from Hodgkin's disease are unusual [1]. The cumulative excess risk of mortality from causes other than Hodgkin's disease is mainly related to second malignancies, cardiac disease, and infection. The relative excess mortality per 100,000 patient years in 794 patients treated in Boston is presented in Table 1 [2].

Table 1. Relative excess mortality after treatment for Hodgkin's disease (n = 794).*

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<th>Cardiac</th>
<th>Infection</th>
<th>Second malignancy</th>
<th>Hodgkin's disease</th>
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<tr>
<td>Relative risk</td>
<td>9.3</td>
<td>9.9</td>
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<td>51.4</td>
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* Ref. [2].
Unfortunately, the leukemias that occur after treatment of Hodgkin's disease are either acute myeloid leukemia or myelodysplasia and have an extremely poor prognosis. Patients treated in this setting often have cytogenetic abnormalities involving chromosomes 5, 7, or 8 and have a poorer outcome than patients with de novo acute leukemia.

Patients treated for Hodgkin's disease are also at an increased risk of developing non-Hodgkin's lymphoma [9, 10]. However, this risk is less clearly associated with the type of therapy and might be related to immunosuppression associated with Hodgkin's disease.

Young women treated for Hodgkin's disease with thoracic radiotherapy are at a high risk for developing breast cancer [11, 12]. The risk of breast cancer appears to be age related, with a relative risk of 56 times for those patients 19 years or younger at the time of treatment, seven times for those 20–29 years of age at the time of treatment and no increased risk for those patients 30 years of age or older [11]. In contrast to leukemia, the breast cancers that occur in patients treated with Hodgkin's disease do not appear to have a poorer prognosis than breast cancer developing de novo (Table 2). However, they are more often bilateral or involve the medical aspect of the breast. The high risk of breast cancer should lead to intensified screening in these patients [13].

Patients who received thoracic radiotherapy are also at an increased risk of developing lung cancer. This risk is increased considerably if patients smoke. Part of the long term follow up in patients with Hodgkin's disease should include discouraging patients from smoking. The increased risk of lung cancer might also be related to exposure to alkylating agents.

A variety of other cancers have been reported to be increased in patients treated for Hodgkin's disease with radiotherapy and/or chemotherapy. These include sarcomas, malignant melanomas and thyroid cancer [7, 10, 14].

**Table 2** Characteristics of breast cancer after irradiation for Hodgkin's disease.

- Younger age.
- More bilateral cancers.
- Frequent medial location.
- No difference in prognosis.

Other organ injury

Injury to a number of organ systems can lead to long-term morbidity and mortality in patients treated for Hodgkin's disease. These include immune dysfunction, cardiopulmonary disease, bone disease, and endocrine and gonadal dysfunction.

Patients who undergo a splenectomy as part of the evaluation for treatment of Hodgkin's disease are at an increased risk for serious infections [15]. Serious infections with Streptococcus pneumoniae has been reported to occur as high as 7% of such patients. This infection is frequently fatal. Patients should be vaccinated against Streptococcus pneumoniae infection before undergoing splenectomy. Many physicians would also encourage long-term antibiotic use in young patients who undergo splenectomy.

A variety of other infections have been reported to be increased in patients who have been treated for Hodgkin's disease. The most frequently seen is Herpes zoster infection. In fact, in the past, the scars of Herpes zoster were suggested to be a characteristic physical finding in patients who had Hodgkin's disease. Herpes zoster develops in 11%–27% of patients in the few years following the treatment of Hodgkin's disease [15].

Mediastinal radiation is a major risk factor in the development of cardiac disease following the treatment of Hodgkin's disease. With older radiation techniques utilizing predominantly anterior fields, radiation related pericarditis was a major problem. This is much less important with modern radiotherapy techniques. However, accelerated atherosclerosis and coronary artery disease appears to remain a significant risk factor. The relative risk of death from cardiac disease following treatment for Hodgkin's disease has been estimated to be 3.1 times [1, 2]. The highest risk is in patients treated with radiotherapy before the age of 20 [16]. Adriamycin has become an important drug utilized in such regimens as ABVD for the treatment of Hodgkin's disease. The long-term effect of adriamycin on the heart in these patients remains to be determined.

Lung disease following treatment for Hodgkin's disease can take several forms [17, 18]. Radiation pneumonitis develops in the first few months following radiotherapy and seems to be increased in frequency when combined modality therapy and larger treatment fields are utilized [19]. Radiation pneumonitis is usually self limited; however, it can require treatment with corticosteroids. This can present complicated management problems and it is often difficult to completely taper patients off steroids.

Osteonecrosis can occur in up to 10% of the patients treated with combined modality therapy for Hodgkin's disease [20, 21]. This condition has considerable morbidity and can lead to joint replacement to manage chronic pain. Decreased bone density has been reported in both men and women following treatment of Hodgkin's disease [22, 23]. Radiotherapy to sites of active marrow can lead to long term aplasia in irradiated sites [24].

Thyroid disease following radiation to the neck is a frequent problem in patients treated for Hodgkin's disease [25]. In a large series, the incidence of hypothyroidism has been estimated to be 31%. In addition to hypothyroidism, hyperthyroidism is also known to occur [25]. Approximately 2% of the patients treated with radiotherapy to the neck will develop Graves disease.

Gonadal dysfunction is a well known complication in the management of Hodgkin's disease. When extended field radiotherapy was a major treatment this was a sufficiently significant problem in women to make
Late complications associated with high-dose therapy and autotransplantation

Patients undergoing high-dose therapy and autotransplantation have the long term risks associated with their initial therapy for Hodgkin's disease in addition to the high-dose therapy that preceded the transplant. Secondary malignancies in these patients have mainly been treatment related leukemias. In one large series the actuarial risk of developing leukemia was approximately 10% of patients with Hodgkin's disease undergoing autotransplantation [28]. The risk was not related to age. It is difficult to ascertain the contribution of the high-dose regimen to leukemia risk, since these patients had been exposed to MOPP-like regimens before coming to transplant.

The incidence of other complications following high-dose therapy and autotransplantation for Hodgkin's disease are similar to those seen after standard dose therapy. In one large series of patients with both non-Hodgkin's lymphoma and Hodgkin's disease who underwent autotransplantation, hypothyroidism developed in 16% [28]. Cataracts were seen in 6% of patients and was restricted to patients receiving total body radiotherapy. The majority of patients were able to return to their normal activities, but approximately 10% had a reduced activity level on follow up. These patients were most likely to be those that had recurrence of their lymphoma.

Sexual dysfunction was a major problem following high-dose therapy for lymphoma [28]. However, this complication can also be seen after standard dose therapy, and the added risks of high dose therapy are difficult to estimate. Approximately one-third of patients after high-dose therapy for lymphoma report a diminution in sexual desire, and 20% of men in complete remission following the procedure had a reduced ability to achieve erection.

Late infections after autotransplantation were frequent. Herpes zoster infection was seen in 24% of patients, pneumonia in 12%, and urinary tract infections in 10% [28].

Conclusion

The frequency of long-term complications in patients treated for Hodgkin's disease makes continued follow-up an important part of their care. This careful follow-up should include efforts to prevent morbidity and mortality by early diagnosis and attention to risk factors. Women who receive thoracic radiotherapy should have regular mammograms instituted at an earlier age than usually recommended. Smoking should be strongly discouraged. Thyroid disease needs to be anticipated and diagnosed early.

Future regimens for Hodgkin's disease need to take into account both long-term complications of therapy as well as the effectiveness of the treatment in curing Hodgkin's disease. While a lower cure rate would not be acceptable, reducing late toxicity is an important goal.

References

11. Aisenberg AC, Finkelstein DM, Dopple KP et al. High risk of

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<th>Regimen</th>
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<td>MOPP-like</td>
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