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Four Patients with Recurrences of Hodgkin's Disease After 15 Years or More

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LONG-TERM SURVIVORS of Hodgkin's disease have an increased risk of dying in comparison to the standard population [1, 2]. Second malignancies, intercurrent diseases and cardiac failure are the main causes of death. This means that patients require follow-up for a very long period after the treatment. Some patients may develop recurrent Hodgkin's disease many years after they have reached complete remission. This report discusses tumour regrowth in 4 patients after a tumour-free interval of at least 15 years.

Patient 1, a female, was referred to our hospital in January 1961. A mediastinal mass was found in November 1959. The erythrocyte sedimentation rate (ESR) was elevated. At thoracotomy a tumour was found above the right hilus. Histology of the biopsy showed nodular sclerosing Hodgkin's disease. Approximately 1 year later the mediastinum became more enlarged. The patient was irradiated to a dose of 30 Gy by two opposing fields in 18 fractions with orthovoltage therapy (250 kV). In 1964 there was a recurrence of nodular sclerosing Hodgkin's disease in the left neck. This area was treated with orthovoltage therapy; she received 25 Gy in seven fractions. Follow-up was performed mainly in the local hospital. The patient then presented with tumour recurrence in the lower part of the sternum with a fistula into the left upper abdomen in 1981, that is 17 years after the last treatment. Histology again showed Hodgkin's disease, nodular sclerosis. She was treated with six cycles of mechloretramine, vincristine, procarbazine, prednisone (MOPP), which led to regression of the tumour mass. The patient was then irradiated on the side of the original tumour recurrence to a dose of 30 Gy by megavoltage therapy. In July 1986 histologically proven recurrences—Hodgkin's disease, nodular sclerosing type—developed in the nasopharynx, the left side of the neck and thereafter in the groin and lung. She died in December 1989.

Patient 2, a male, born in 1920 was diagnosed with Hodgkin's disease, nodular sclerosing subtype, stage 1A, in 1955. He was irradiated on both axillae to a dose of 7 Gy and on both sides of the neck to a dose of 9 Gy by orthovoltage radiotherapy. Recurrent Hodgkin's disease—heralded by coughing and dyspnea—developed in the right hilum of the lung and mediastinum in April 1988. Subtyping was not possible now due to the small size of the mediastinal biopsy specimens. The patient was in complete remission after chemo- and radiotherapy until the most recent follow-up date in April 1993.

Patient 3, a woman born in 1933, was treated in another hospital for Hodgkin's disease, nodular sclerosing type, in the left supraclavicular lymph nodes and the left upper mediastinum in 1962. She was irradiated on those areas with 250 kV therapy to a dose of 20 Gy in 10 days, 2 Gy per fraction. The disease recurred in 1981 in the right side of the mediastinum. Histology appeared to be again nodular sclerosing type. She died in September 1986 after bone marrow recurrence.

Patient 4 was 19 years of age when he presented in 1976 with Hodgkin's disease, stage 1E involving the mediastinum and chest wall. Histology was most consistent with the mixed cellularity subtype. Staging procedures did not show tumour activity. The patient received a dose of 40 Gy with megavoltage radiotherapy in 4 weeks to a mantle field, followed by the same dose to the paraaortic region. Recurrent tumour was detected in 1991 when he was investigated following 2 months with fever and weight loss. The lymph nodes in the iliac region and the bone marrow were involved. The histological subtype again was difficult to determine, but was most likely nodular sclerosis. Treatment with six alternating cycles of combination chemotherapy produced a partial remission.

Of the 4 patients, 3 received a form of therapy which is far from optimal as judged nowadays. In spite of this, the natural behaviour was a very slow process. Although theoretically it might be possible that the patients had a new disease, the similarities of the histology in 2 cases do support the probability of tumour recurrence.

Bodis published recently the 10- and 15-year cumulative probability rates of late relapse in 5-years disease-free patients of 4.8 and 8.5%, respectively. These early stage Hodgkin's disease patients had been treated according to one of three EORTC protocols, which yielded cure rates greater than 80% [3].

Relapse-free survival curves show almost a plateau after 6 years for all clinical stages [4], which may flatter reality for at least some patients. The pattern of Hodgkin's disease recurring after a very long disease-free interval suggests the possibility that at least in some patients the tumour doubling times are very slow. Another hypothesis could be that these patients in seemingly complete remission live in symbiosis with clinically undetectable tumour. The nature of the factor which upsets this balance between tumour and host is unknown. Strum has formulated this concept in his report about the persistence of Hodgkin's disease in long-term survivors [5]. At autopsy in 18 patients, evidence of tumour was observed in 16, even in those dying from unrelated causes. A third possibility could be that in these long-term survivors of Hodgkin's disease the so-called recurrence is in fact a second primary tumour. This, however, in our opinion seems less probable.

It is essential to perform biopsies when a patient treated for Hodgkin's disease has signs of tumour regrowth. Morphological examination is necessary to prove that the patient is suffering from recurrent Hodgkin's disease, and to exclude the presence of a second malignancy such as non-Hodgkin's lymphoma or other neoplasms, since it is known that Hodgkin's disease patients are at a high risk for second malignancies induced by therapy [6].

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In conclusion, there are patients with Hodgkin's disease who develop tumour recurrence after a very long period of clinical complete remission. It is recommended that these cases are collected to learn more about the features of this disease.

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Phase II Study of Tauromustine in Disseminated Malignant Melanoma

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THE GLOBAL incidence of malignant melanoma (MM) is continuously increasing, most rapidly in Scandinavia with a 5% rise each year [1, 2]. The best response rates after chemotherapy or immunotherapy are 20–25%, with a median survival gain of only approximately 6 months [3, 4]. Tauromustine (TCNU) has been proven to have some antitumour effect on patients suffering from MM, and is well tolerated [5]. The objective of this study was to determine whether the response rate in patients with MM could be increased by employing a weekly dose schedule of TCNU [6].

Patients between 18 and 75 years of age, with histologically proven malignant melanoma, and with measurable and evaluable disease not amendable to curative surgery or radiotherapy, were included in this open phase II study. Other inclusion criteria were progressive disease, performance status of 2 or less, life expectancy of at least 3 months and normal liver, renal and bone marrow functions. All patients gave their informed consent to participate in the study, which was approved by the national board of health and the ethical committees. The dose of TCNU was 50 mg/m^2/week. Blood counts were monitored weekly. Patients were evaluated for response every 8 weeks, and the treatment was continued until progressive disease (PD) was observed. Dose reduction due to haematological toxicity was performed, as reported previously [6]. Response and toxicity were graded according to the WHO recommendations [7]. TCNU was supplied by Kabi Pharmacia Therapeutics AB (Helsingborg, Sweden) in tablets of 10, 20 and 50 mg.

Between October 1990 and October 1991, 56 patients entered the study. 2 patients were non-eligible (performance status 3). Among the 54 eligible patients, 2 left the trial after 2 and 3 weeks, respectively, due to concurrent disease. Thus, 52 patients (30 males and 22 females) were evaluable for response.

The median age was 60 years (range 24–72). Prior treatment comprised surgery (52 patients), regional perfusion with melphalan (1 patient) and radiotherapy (9 patients). Dominant sites of disease were visceral (28 patients), soft tissue (23 patients) and bone (1 patient). 34 patients had PD, including 2 early deaths, 11 had stable disease, 4 had a partial response and 3 had a complete response, yielding a response rate of 13.5%. Four of the responses occurred in patients with soft tissue disease, and 3 in patients with visceral disease. Median time to progression was 30 weeks (range 16–95) for responders, and 8 weeks (range 8–58) for non-responders. Median overall survival for all patients was 5.8 months (range 1–22). The median average dose tolerated was 37 mg/m^2/week over a median time of 9 weeks (range 8–67). Dose-limiting toxicities were thrombocytopenia and leucopenia. Non-haematological adverse effects and haematological toxicity did not differ from what was observed in the phase I study [6].

With this weekly schedule, the tolerable dose of TCNU was 37 mg/m^2/week. This corresponds to a 50% increase in the weekly dose compared with the 5-week schedule [5]. However, this did not translate into an increased response rate, which was 15% with the 5-week schedule [5] compared with 13.5% in the present study. The patient characteristics were not significantly different in the two studies in terms of age, sex, location of metastases or performance status, nor were they different from patients as such with MM [6, 8].

The median disease-free interval from diagnosis to start of TCNU medication was 1.9 months (range 0–13.8) for non-responders; for responders and patients with stable disease it was 2.2 months (range 0–21.8), a difference which is not statistically significant. The median survivals of these two groups were 4.0 and 9.7 months, respectively, indicating that TCNU in some patients may have reduced the progression rate of melanoma lesions.

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