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High-dose Therapy Followed by Autologous Bone Marrow Transplantation in Previously Untreated High Grade Non-Hodgkin's Lymphoma: 10-year Long-term Results

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THE ADVANCES in therapy for high grade non-Hodgkin's lymphoma (HG-NHL) have improved the long-term outlook for patients with this disease. Over the past 10 years, durable remissions have been achieved in an increasing proportion of patients with HG-NHL, and there is evidence that remission rates and survival may be improved by using intensive chemotherapy regimens [1, 2].

In 1986, we reported [3] on the role of induction high-dose therapy followed by autologous bone marrow transplantation (ABMT) in previously untreated HG-NHL. From April 1982 to March 1985, 13 patients underwent high-dose therapy followed by ABMT with BAEC (BCNU, 200 mg/m^2 on day −2; cytarabine, 150 mg/m^2 every 12 h on day −4 to −1; etoposide, 150 mg/m^2 every 12 h on days −4 to −1; cyclophosphamide, 45 mg/kg on days −4 to −1) as a conditioning regimen. Mean age was 28.5 years (range 18–47), there were 9 males and 4 females, and 9 had bulky disease. After ABMT, patients received a consolidation therapy including both radiotherapy on the bulky mass and three phases of chemotherapy. All patients experienced a large cytoreduction and 9 (69%) achieved a complete remission; neither therapy-related deaths nor life-threatening complications were recorded. 2 patients relapsed, 4 and 26 months after transplant, respectively, without bone marrow involvement.

Currently, with a median long-term follow-up of 132 months (range 115—150 months), 7 patients are still without evidence of lymphoma and, in view of the biological behaviour of their aggressive disease, may probably be defined as cured. In Figure 1a we report the overall survival curve of all 13 patients and Figure 1b shows a relapse-free survival curve for all the patients beyond 100 months.

Conventional combination chemotherapy, independently by first-, second- or third-generation regimens, has transformed HG-NHL from a fatal disease to one that is now often curable.

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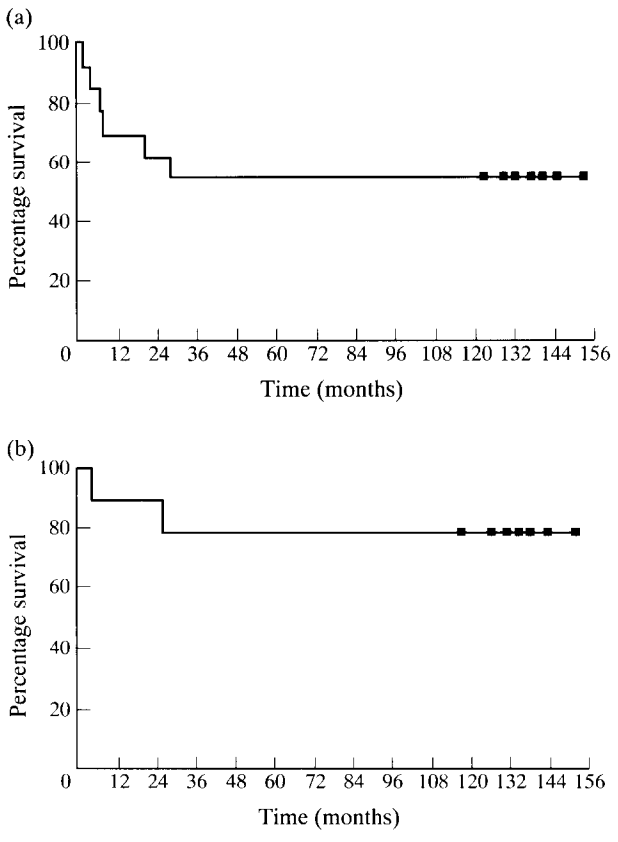

Figure 1. (a) Overall survival curve of 13 HG-NHL patients who underwent high-dose induction therapy. (b) Relapse-free survival curve of 9 HG-NHL patients who obtained complete remission after ABMT at diagnosis.

One could conclude from the Fisher randomised trial [4] that CHOP (cyclophosphamide, doxorubicin, vinicristine, prednisone) should be considered standard therapy for patients with HG-NHL. However, all HG-NHL patients are not alike, and certain subsets of poor prognosis patients can be identified in all the chemotherapy trials. The recent International Prognostic Index [5] has identified a number of characteristics that define several subsets of patients based on their overall and disease-free survival. Probably early use of high-dose chemotherapy with ABMT or peripheral stem cell transplantation in the poor prognosis patient population may improve the long-term outcome for this patient group.

Since high-dose therapy has not yet been proven beyond any doubt to be superior to conventional therapy [6,7] in any setting for HG-NHL, it should be given in carefully designed clinical trials. The real pressing issue is the value of high-dose as primary therapy in particular subsets of patients with poor clinical (according the International Prognostic Index) and biological (proliferation index, p53, apoptosis, MDR, etc.) prognostic features. Large clinical trials need to be conducted comparing this approach with conventional therapy in poor-risk patients as defined by the International Prognostic Index.

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Routine Bone Scan and Serum Alkaline Phosphatase for Staging in Patients with Renal Cell Carcinoma is Not Cost-effective

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In the Netherlands, a total of 1290 new cases of malignant renal tumours were reported in 1990 [1]. Of all renal tumours, 80–85% are renal cell carcinoma (RCC) and these account for 3% of all adult malignancies. Since 1930, the incidence and mortality of RCC have increased both for males and females. However, the rate of increase in mortality is less than the rate of increase in incidence [2]. Whether this is due to improved treatment for patients with RCC or due to wider application of screening methods, such as abdominal ultrasound, by which patients are selected in an earlier stage of RCC, is still unknown. The question of whether one should perform radical nephrectomy in patients with metastatic disease is still unanswered. According to some authors, nephrectomy improves survival in patients with metastatic RCC when some of the prognostic factors, such as solitary metastases (especially in the lung) or a low grade tumour are present [3,4]. Others revealed that nephrectomy increased survival only in those patients with bone metastases exclusively [5].

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These considerations make it clear that the optimal treatment choice depends very much on accurate pre-operative staging. Until recently, the standard staging procedure included ultrasound of the kidneys, CT scan of the abdomen and thorax, radionuclide bone scan and laboratory tests. To evaluate the results of a routine pre-operative bone scan and measurement of serum alkaline phosphatase (AP) in staging patients with RCC, 107 patients were evaluated from 1985 until 1993.

There were 61 males, median age 62 years (range 2–83) and 46 females, median age 63 years (range 18–81). 101 patients had a radical transabdominal tumour nephrectomy and a facultative regional lymph node dissection. Due to metastatic disease to lungs and bone, 6 patients did not undergo surgery. Pre-operative investigations included laboratory tests, ultrasound of the kidneys and CT scan of the abdomen and thorax. Urography was optional. AP was measured using the IFCC (International Federation of Clinical Chemistry) method with an AMP buffer at 37°C, reference value (13–120 U/l). In all 107 patients, a routine pre-operative bone scan with Tc-99m-MDP (Technetium Methylene Diphosphonate) 580 MBq was performed. Three to four hours after injection, whole body scans, and if considered necessary, detail images, were obtained. Hot spots on the bone scan were further evaluated by radiography of the affected sites.

Patients were followed from 24 until 144 months with a median of 70 months. Of the 107 patients with a pre-operative bone scan, 21 had suspicious lesions. 8 patients had a positive bone scan confirmed by osteolytic lesions seen on radiography. 13 patients had hot spots on the bone scan and were further evaluated by radiography of the affected sites. In all 13 patients, the lesions complied with degenerative abnormalities. 86 patients had a negative bone scan. Together with the 13 false positive scans, this accounts for a percentage of 92.5%.

When we divided patients into two groups of normal and elevated AP level, 71% has a normal AP and 29% has an elevated AP. In the group with a normal AP, values ranged between 39 U/l and 116 U/l, with a mean value of 81 U/l and a standard deviation of 17 U/l. In the patients with an elevated AP, values ranged between 123 U/l and 492 U/l, with a mean value of 227 U/l and a standard deviation 107 U/l. In 3 of the 8 patients with a positive bone scan, AP was elevated. However, in the patients with an elevated AP, only 10% had a positive bone scan. In the group of patients with normal AP levels, 6.5% had a positive bone scan (Figure 1).

From the patients with an elevated AP and a normal bone scan, 43% (12/28) had a normal AP level after nephrectomy within 6 months. These patients are still alive with no evidence of disease with a mean follow-up of 61 months. Another 21%

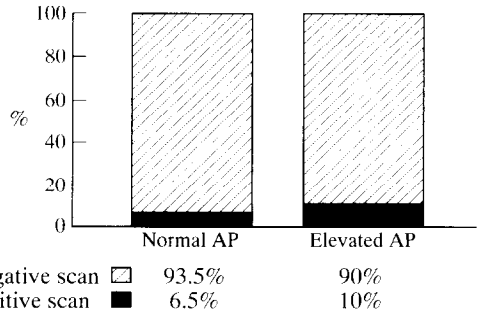

Figure 1. Results of bone scans in patients with normal (n=76) and elevated (n=31) alkaline phosphatase (AP) levels.