total body irradiation and this enzyme changes may lead to functional alterations. On the basis of experience from conventional radiotherapy it seems possible that coronary artery disease or myocardial infarction may occur at an earlier age than normal in this patient population (77).

Second tumour induction

In the first year or two after bone marrow transplantation, the commonest malignancies seen are recurrence of the original disease or lymphoproliferative disorders which seem to be related to immune suppression and Epstein Barr virus infection (78).

A large study from the Seattle Group and the International Bone Marrow Transplant Registry has followed nearly 20,000 patients treated with bone marrow transplantation to determine the risk of the new solid cancer. 9,501 patients survived longer than 1 year and 73% of the patients had had TBI as part of the initial conditioning for BMT. 3,200 patients have survived for 5 years or more and in this group 80 second tumours were diagnosed These included 17 carcinomas of the buccal cavity or pharynax, 11 brain tumours, 11 melanomas, 8 thyroid carcinomas, tissue tumours. The overall risk of developing a second tumour was inversaly related to the age at the time of bone marrow transplant and directly related to time since treatment, original tumour type and dose of radiation (79).

Risk in children treated before the age of 10 was increased 36.6 times and as age 20-29 4.6 times, whereas over the age of 39 the risk was nearly the same as in a normal population. Cumulative incidence was 0.7% at 5 years, 2.2% at 10 years and 6.7% at 15 years. Patients with ALL were most likely to develop brain tumours whereas melanoma occurred more often in those treated for AML. Patients treated with thoracoabdominal or total body irradiation had a higher risk than those conditioned without radiation. No difference was seen whether TBI was given as a single fraction on in several fractions. The risk of brain tumours was highest in those who had received cranial as well as total body irradiation (4 of the 13 patients with brain tumours).

Other factors which are possibly associated with increased risk may be determined by immunological abnormalities: T cells depletion possibly related to melanoma induction, immune abnormalities with oral mucositis and chronic graft versus host disease for buccal cavity tumours, cyclosporin administration (for skin tumours), papilloma virus infection i squamous cell carcinomas of skin and buccal mucosa. Buccal cavity tumours observed were muco-epidermoid carcimonas – the type also observed in survivors of the atomic bomb.

It is interesting to compare this patteren of second tumour incidence with that seen after treatment of leukaemia without bone marrow transplant when the cumulative incidence of second tumours at 20 years is 2.9-4%. A similar pattern of brain, thyroid, skin, and connective tissue tumours occurs, but the greatest risk (27 times expected) is of brtain tumours in those treated with cranial irradiation (80).

These date underline the risks of radiation and the need for prolonged follow-up. Patients should be encouraged to avoid exposure to known carcinopgens (such as tobbaco) which may potentiate the effects of radiation.

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NEW ADVENCES IN BIOLOGY AND MODERN TREATMENT OF HODGKIN'S DISEASE

Volker Dieh

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LOCALISED AND ADVANCED HODGKIN'S DISEASE: TOWARD A COMMON STRATEGY? AN EORTC LYMPHOMA GROUP POINT OF VIEW

Patrice Carde

Paryż

In patients with localised Hodgkin's disease (HD), the EORTC initiated in 1975, with the H5 trial a completely new strategy consisting in adapting treatment intensity (NCI Monographs 6: 303-310,

1988; JCO 6: 239-252, 1998) to prognostic factors that had been prospectively identified in the previous trials (Int J Radiation Onc Biol Phys 11: 23-30, 1985; Blood 73: 47-56, 1989), together with response-related indicators (JCO 6: 596-602, 1988; Am J Hematol 37: 253-257, 1991; Ann Intern Med.114: 361-365, 1991).

In favourable patients, the extension of this strategy in the H6F trial allowed to spare them not only the adjuvant chemotherapy (CT) but also laparotomy, establishing subtotal nodal irradiation (STNI) as a new standard in clinically staged patients (ASH 1992; JCO 11: 2258-2272, 1993). In the subsequent trials (H7F, H8F), brief combined non-toxic CT regimens with radiotherapy restricted only to the involved-field (IF RT) provided superior freedom from progression (FFP) and at least comparable overall survivals (OS) to(S) TNI.

In unfavourable patients, in the H5U trial, combined CT/RT modalities, preferably with an adriamycin-containing regimen, provided better results than TNI. In the subsequent H7U and H8U yrial, treatment adjustments balanced the respective intensitiesof CT and RT: treatment de escalation proved dangerous.

In advanced stage disease, an earlier trial suggested that early response could be used to adapt treatment modality and length (JCO 6: 596-602, 1988; JCO 12: 279-287, 1994). In the subsequent trial, this observation has been successfully utilized for the early salvage of relapses (Ann Oncol 2: 63-66, 1991) or poor responders(Ann Oncol, 1997) and the important question of adjuvant RT is being investigated in a randomised way.

Underlying all HD trials, two basic concerns sustain the EORTC strategy, that encompass all patients with HD. One is the need for permanent and prospective assessment of prognostic factors, with which treatment continuously interacts; in this respect a continuum may exist between "localised" and "advanced" HD. The other is aiming at the best possible treatment intensity adaptation to patient's requirements for the sake of sparing short and long- term toxicities including those measured by function and Quality of Life impairments. Combined modalities, including intensive ones, may remain the best options for these tasks. The role of RT may persist in all patients categories, and that of immunotherapy may develop, in parallel to the better understanding of HD natural history.

Working together with newly cooperating countries, like Poland, will allow a markedly better understanding of early and late treatment effects, conditions for continuing to improve the care for our patients.

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NEW APPROACHES TO FOLLICULAR LYMPHONA

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With conventional therapy, follicular lymphona remains incurable for most patients. An experimental approach is therefore justified.

Recognition of the association between follicular lymphona and the (14;18) translocation and the possibility of detecting residual disease at the molecular level using the polymerase chain reaction (PCR), have led to the concept of 'molecular remission'.

Several new approaches, some of which have been reported to result in 'molecular remission' eg. the chimaeric antibody antti-CD20 and the combination Fludarabine, Mitoxantrone and Dexamethasone are currently being evaluated at SBH. These and other treatment options, including high dose treatment (Cyclophosphamide + total body irradiation) supported by autologous haemopoietic progenitor cells, radio-labelled anti-CD20 and the nonmyeloablative regimen comprising Fladarabine and Cyclophosphamide supported by allogeneic bone marrow transplantation will be discussed.