Introduction

An overview of the Fifth International Symposium on Hodgkin’s Lymphoma

Recent advances in basic and clinical research

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The Fifth International Symposium on Hodgkin’s Lymphoma was held in Cologne, Germany, between September 22 and 25, 2001. More than 600 physicians and scientists from 48 countries attended this symposium, organized by the German Hodgkin’s Lymphoma Study Group (GHSG), and chaired by Professor Volker Diehl from the University of Cologne. The scientific program covered a broad range of pre-clinical and clinical topics in the field of Hodgkin’s disease (HD) and provided a comprehensive update of scientific and clinical progress. The ‘state of the art’ with regard to recent scientific achievements has been presented by well-known experts. This symposium aimed to serve as an outstanding forum dedicated to basic and clinical research in HD. This introduction summarizes the essential findings presented in Cologne.

Epidemiology and biology

A major impact in our understanding of the biology of HD was achieved by molecular single-cell studies, which showed that HRS cells mostly represent clonal populations of transformed germinal centre (GC) B cells, in very rare cases also of T cells. However, although the cellular origin of Hodgkin and Reed–Sternberg (HRS) cells now has been elucidated, the mechanism of transformation still is not understood. The role of constitutive activity of nuclear factor (NF)-κB in malignant transformation has been further investigated, and activation of Notch 1 signalling was implicated to be involved in the regulation of NF-κB in HRS cells. Furthermore, constitutive STAT3 signalling is suggested to contribute to growth deregulation of HRS cells. Allelotyping of single HRS cells reveals allelic losses in small areas of particular chromosomes, pointing to the possible presence of a tumour suppressor gene in these areas. Another characteristic of HRS cells is their grossly hyperploid karyotype and the co-existence of B and dendritic cell-type gene expression. Despite previous speculations that cell fusion was the underlying mechanism, this does not seem to have a role in the generation of the HRS cell tumour clone (Küppers et al., in this issue).

Although the search for an HD virus has not yet been successful, epidemiological and clinical data suggest an infectious agent. The role of Epstein–Barr virus (EBV) in the pathogenesis of HD has been investigated, but is still poorly understood. Infectious mononucleosis increases the risk of HD three-fold. Furthermore, a risk factor for developing EBV-positive HD seems to be delayed exposure to EBV. The putative infectious agent in EBV-negative HD, however, remains elusive (Jarrett, in this issue).

Pathology

Despite the impressive advances in the field of lymphoma diagnostics and the establishment of new classifications, some cases still remain unclassifiable. These cases exist in a diagnostic ‘grey zone’ between HD and some other lymphoid neoplasms, including the T cell-rich large B cell lymphoma (TCRBCL), lymphocyte predominant HD (LPHD) and the lymphocyte-rich classical HD (LRCHD). It has been shown that morphological, immunohistological and molecular investigations cannot differentiate all of these cases. Owing to their relatively low incidence, clinical data from larger patient populations are difficult to obtain, and large-scale clinical studies are lacking. Therefore, this symposium aimed to give a comprehensive overview of the clinical data on these three entities, and to prove that the pathological differentiation is not merely of academic interest, but of clinical relevance. Uniform criteria for the diagnosis of TCRBCL, closely related to nodular lymphocyte predominant HD (NLPHL) have not been established, and further investigations are warranted (Rüdiger et al., in this issue).

Prognostic factors

Prognostic factors are useful for developing risk-adjusted therapies, especially in the light of 20% to 25% of Hodgkin patients who fail primary therapy. Although historically some
candidate factors have been named, findings have not been consistent. A comprehensive overview on these factors is given by Zander et al. (in this issue). The hypothesis that prognostic factors are resolving due to successful adaptation of treatment strength to the individual disease burden of the patients is also discussed (Hasenclever, in this issue).

**Early stage HD**

In early stage HD, the role of radiation therapy has changed greatly in the last few decades. Presently, it is primarily used as consolidation therapy after chemotherapy. The concept of combined modality treatment mandated a reassessment of the radiation field in HD. The main focus has to be on the reduction of field size and dose. In this issue, Yahalom and Mauch present new guidelines for delineating the involved field (IF) in HD and demonstrate that IF is the standard radiation field for patients with early and advanced-stage disease following chemotherapy.

Radiotherapy, especially extended field (EF) irradiation, has been recognized as a significant contributor to late-term toxicities. To overcome this risk the National Cancer Institute of Canada-Clinical Trials Group (NCIC-CTG)/Eastern Cooperative Oncology Group (ECOG) presented a randomised phase III study comparing radiotherapy or ABVD (combination chemotherapy with doxorubicin, bleomycin, vinblastine and dacarbazine) plus radiotherapy versus ABVD alone. Results will be expected in 2002. O. Press presented a SWOG/CALGB randomised trial of subtotal lymphoid irradiation versus doxorubicin, vinblastine and subtotal nodal irradiation (STLI). Both regimens were well tolerated and yield excellent overall survival. Freedom from treatment failure (FFTF) was better in the combined modality treatment group than in STLI alone.

The results of the GHSG studies HD 7 and HD 8 were presented by J. Wolf. It has been shown that 2× ABVD before EF radiotherapy reduces relapse rate (HD 7), and that EF radiotherapy (30 Gy) can be substituted by IF radiotherapy (30 Gy) after 2× COPP/ABVD (HD 8). Thus, the GHSG, like most other major study groups, has dropped EF irradiation as a treatment recommendation for early stage favourable and unfavourable disease (Wiedenmann et al., in this issue).

**Advanced-stage HD**

Numerous randomized clinical trials investigate the best current regimen in advanced-stage HD [11 trials with >2000 patients analyse MOPP (combination chemotherapy with mechlorethamine, vincristine, procarbazine and prednisone) alternatives, 10 trials with >1800 patients combined modality, 10 trials with >2600 patients alternating regimens and seven trials with >3700 patients hybrid regimens]. All major study groups [European Organisation for Research and Treatment of Cancer (EORTC), British National Lymphoma Investigation (BNLI), GHSG, Groupe d’études des Lymphomes de l’Adulte (GELA), Scotland and Newcastle Lymphoma Group (SNLG), Italian, Children’s Cancer Group New York (CCG/NY), Gesellschaft für Pädiatrische Onkologie und Hämatologie (GPHO)] presented their findings at the symposium in Cologne (Carde et al., Connors, Fermé et al., Franklin and Diehl, Chiesi et al., Kelly et al., in this issue).

The final results of the GHSG HD 9 study for advanced-stage HD was presented by V. Diehl. The data from the three-arm randomized trial clearly demonstrated the advantage of escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone (BEACOPP) in terms of treatment outcome, survival and FFTF. Thus, the current GHSG trial HD 12 sets escalated BEACOPP as standard for advanced HD (<65 years). Owing to these results, showing a 3-year survival rate of >95%, the aim of subsequent clinical trials will be to reduce total dose and toxicity. This question is currently being investigated by an European/Canadian intergroup trial using 4× escalated + 4× baseline BEACOPP.

**Refractory/recurrent HD**

Depending on stage and risk factor profile, >80% of patients with HD can be cured with first-line treatment. Patients who relapse have different treatment options depending on the initial treatment. Those alternatives include radiotherapy for localized disease in previously non-irradiated areas, conventional salvage chemotherapy and high-dose chemotherapy followed by autologous stem-cell transplantation (autoSCT). New approaches include sequential high-dose chemotherapy, tandem high-dose chemotherapy, allogeneic stem-cell transplantation (alloSCT) or non-myeloablative conditioning with allogeneic mini-transplants.

It has been demonstrated that high-dose chemotherapy is superior to conventional chemotherapy in chemosensitive patients. The best high-dose chemotherapy regimen, however, is as yet unknown. Dexa-BEAM (BCNU, etoposide, cytarabine, mephalan) has been associated with severe toxicity. A. Engert presented the Cologne sequential high-dose regimen [induction with 2× DHAP (dexamethasone, Ara-C and cisplatin), followed by high-dose cyclophosphamide, high-dose methotrexate + vincristine + high-dose etoposide + BEAM]. DHAP is effective at reducing tumour burden, and acute toxicity is acceptable. However, little is known regarding alloSCT in HD. Owing to immunological problems intrinsic to the development of graft-versus-host disease, the high-transplant related mortality and the poor outcome after alloSCT, auto-SCT has been given priority. In this issue Sureda and Schmitz describe allogeneic low-intensity regimens that have been developed in order to reduce transplant-related mortality.
**Immunotherapy**

Although enormous progress in the treatment of HD has been achieved, there is still a significant percentage of patients who relapse or progress and do not respond to further therapy. The rationale for selective immunotherapy of Hodgkin’s lymphoma is the poor prognosis of relapsed patients and long-term toxicity of standard therapy. Future approaches unclude the use of monoclonal antibodies, immunotoxins, radio-immunoconjugates, bispecific antibodies and recombinant constructs.

The treatment of HD patients with monoclonal antibodies is under current investigation at the University of Cologne, and the initial results seem to be promising.

Another approach is T cell therapy. EBV protein is present in the malignant cells of ~40% of all Hodgkin’s cases, and provides a target for immunotherapy with cytotoxic T lymphocytes. Owing to the ability of Hodgkin’s tumours to avoid cytotoxic T lymphocytes, specific strategies to overcome this obstacle have been employed (as presented by C. Rooney).

**Sequela of treatment/quality of life**

As a high percentage of patients with HD will be cured, long-term toxicity will become more apparent. Secondary leukemias, non-Hodgkin’s lymphoma, coronary artery disease and sexual dysfunction are the most common. Among these, second malignancies are the most serious. Thus, reduction of treatment-related toxicity is an essential goal.

**Patient seminar**

For the first time a patient seminar with 240 patients has been organized with great success. Four outstanding experts discussed the entities Hodgkin’s lymphoma, low-grade non-Hodgkin’s lymphoma, high-grade non-Hodgkin’s lymphoma and chronic lymphocytic leukemia with the patients at great length.

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