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Meeting Highlight

Third International Symposium on Hodgkin's Lymphoma in Köln, Germany

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INTRODUCTION

THE THIRD International Symposium on Hodgkin's Lymphoma was held in Köln, Germany, between September 18 and 23, 1995. During this meeting, more than 500 participants discussed recent developments in this disease.

BIOLOGY AND MOLECULAR PATHOLOGY

Current aspects in this field were extensively discussed during a preceding workshop on biology and throughout the meeting. The main controversies related to the question of origin and clonality of the mononucleated Hodgkin, and multinulceated Reed/Sternberg (H-RS) cells. Due to the small number in Hodgkin's lymphoma tissues, the origin of H-RS cells has been a matter of discussion for several decades. Lymphocytes of both T-cell and B-cell lineage as well as macrophages and dendritic cells have been considered as potential precursors. New techniques including Southern blot hybridisation and polymerase chain reaction (PCR) proved insufficient in discriminating clonal rearrangements between H-RS and reactive bystander cells. Thus, the recently developed single cell PCR-technique was applied to analyse H-RS cells at the single cell level. During the meeting, four different groups presented their most recent data using different detection methods. Two groups, Küppers and associates and Hummel and associates, isolated single cells from frozen immunostained tissue sections by micromanipulation and subsequently analysed these cells for immunoglobulin heavy-chain (V_H) and kappa light-chain (V_k) gene rearrangements using family-specific and consensus primer in a seminested PCR technique [1, 2]. In contrast, Trümper and colleagues used cell suspensions prepared from fresh Hodgkin's lymphoma tissue to pick single CD30-positive cells for subsequent analysis [3]. Chan and Delabie prepared single cell suspensions from paraffin-embedded Hodgkin's tissues [4]. The different techniques used might account, at least in part, for the different and contradictory results: Küppers and colleagues detected V gene rearrangements in 11 of 12 cases investigated. They confirmed the clonality of these H-RS cells by identifying identical rearrangements in cells from different sections obtained in five cases. Hummel and Stein, analysing 12 cases with CD20-positive HD, demonstrated clonal rearrangements in 6/12 cases analysed, three of which showed additional polyclonal rearrangements and the remaining six cases polyclonal rearrangements only. Chan and Delabie investigating a total of 10 cases (4 lymphocyte predominance, 6 nodular sclerosis) found a clonal subpopulation amid a polyclonal background in 2 cases. In contrast, Trümper and associates were unable to detect clonal rearrangements in their 10 case analyses. Sample diversity due to the heterogeneity of HD as well as technical pitfalls, such as the loss of primer binding due to somatic mutations, were discussed as possible reasons. To investigate methodological differences, Küppers and associates re-analysed one case from Harald Stein's group which had initially been classified as polyclonal. Upon re-analysis, a clonal VK rearrangement was detected. Thus, a careful re-evaluation with the best technique available is needed before final conclusions about polyclonality can be drawn. Taken together, the current findings suggest that H-RS cells represent a truly monoclonal population which seems to be B-cell derived.

Further support for the monoclonality of the H-RS cells comes from recent data by Weber-Matthiesen and colleagues who reported a newly developed method involving fluorescence immunotyping and interphase cytogenetics as a tool for investigation of neoplasms ("FICTION") to detect numerically aberrant tumour cells that can be identified by interphase cytogenetics. Combining immunostaining for CD30 and the FICTION technique, all of 30 different samples analysed contained numerical chromosome aberrations which in some cases were identical in all H-RS cells.

The analysis of signalling in HD via different receptors belonging to the TNF-receptor superfamily, such as B7-CD28/CTLA-4 or CD30/CD30L, was discussed during the workshop on "Biology". TNF superfamily ligands are involved in the induction of cytokine secretion, upregulation of adhesion molecules, and the activation of antigens and costimulatory proteins (J. Gruss, Berlin, Germany). Since H-RS cells frequently express TNF receptors including CD30, CD40, CD95, CD120a, CD120b and 4-1BB, the interaction between specific ligands and these receptors might contribute to the interaction of these cells with surrounding reactive bystander cells. The CD30/CD30 ligand interaction has very recently been demonstrated to play a critical role in the induction of apoptosis (T. Mak and coworkers). The analysis of CD30 knock-out mice suggests that T-cell apoptosis in the thymus of these animals is completely abrogated. Thus, CD30 might play a very important role in the pathogenesis of HD.

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DIAGNOSTIC PROCEDURES

In 25–30% of patients with supradiaphragmatic early stages, occult infradiaphragmatic involvement, invisible by ultrasound or CT scan, is detected during laparotomy. Currently, laparotomy is still the most precise method to identify occult lesions in the abdomen. However, this procedure is also associated with side-effects such as severe bacterial infections and blood loss (P. Carde, France) and has been omitted in the clinical trials performed by the German Hodgkin Study Group (GHSG) and the EORTC.

A variety of new diagnostic imaging procedures, including magnetic resonance imaging (MRI), positron emission tomography (PET), somatostatin receptor scintigraphy and immunoscintigraphy, have been evaluated in Hodgkin's lymphoma. The rationale for these investigations is to detect spleen and bone marrow involvement without invasive techniques and to discriminate between fibrosis and vital lymphoma in the follow-up after treatment. Using MRI, only a restricted portion of the body can be investigated. Thus, MRI is usually applied to clinically suspected areas. PET with ^{18}fluorodeoxydeoxy-glucose (FDG) allows the visualisation of metabolic activity throughout the body. PET might become a useful new tool for staging and follow-up of HD. Though initial studies as reported by Bangerter and colleagues [6] are promising, more clinical experience is needed to confirm the general value of this technique.

RISK FACTORS

Another very important unsolved question in HD is the identification of patients at high risk for subsequent treatment failure. In early and intermediate stage HD, factors such as constitutional symptoms, mixed- or lymphocyte-depleted histology, number of supradiaphragmatic sites >4, age above 40 years, and male gender have been associated with an unfavourable prognosis as G. Canellos, Boston, pointed out. D. Hasenclever from Leipzig, Germany, presented a preliminary analysis from the International Prognostic Factors Project on Advanced HD. Data from more than 4000 HD patients entered in different clinical trials worldwide had been collected. Based on these data, a multivariate model using eight different clinical and laboratory variables seemed to predict accurately an individual patient's freedom from treatment failure (FFTF). However, only approximately 5% of all patients were predicted to have a 5 year progression-free survival of less than 50%. Thus, the identification of only a small proportion of patients who would benefit from high-dose therapy might become feasible in future trials.

TREATMENT OF EARLY AND INTERMEDIATE STAGES

The long-term disease-free survival in early stage Hodgkin's lymphoma approaches 90%. Since it is unlikely that outcome will be further and substantially improved, a major goal for this group of patients is the reduction of toxicity. Second malignancies, including solid tumours, acute leukaemias and non-Hodgkin's lymphoma, were reported by M. Henry-Amar, Villeneneuf, in up to 70% of patients after 15 years. In particular, combined modality treatment involving MOPP-based regimen and radiotherapy is associated with a high incidence of solid tumours. One approach to reduce toxicity would be to identify cytostatic drugs that are both effective and less carcinogenic. Since ABVD has provided equivalent or superior results to MOPP, MOPP/ABVD or ABVD alone are being regarded as standard thus far. In an approach to circumvent both anthracyclines and alkylating agents, the Stanford group as reported by D. Longo, Frederick, has piloted the VBM regimen (vinblastine, bleomycin, methotrexate) which, however, has been associated with increased pulmonary toxicity in subsequent trials performed by the BNLI [7]. Other regimens which attempt to reduce bleomycin-induced pulmonary toxicity include EVA (etoposide, vinblastine, doxorubicin) or NOVP (novantrone, vincristine, vinblastine, prednisone).

Reducing overall toxicity can be achieved by the reduction of both radiotherapy and chemotherapy. The question of optimal dose and volume of radiotherapy is still a matter of discussion. If radiotherapy is used alone in early stages, most groups currently recommend extended field (EF) technique with an additional involved field (IF) boost. The HD 4 trial of the GHSG as reported by V. Diehl suggests equivalent results between 40 Gy EF and 30 Gy EF plus 10 Gy IF after 2 cycles of COPP/ABVD [8]. However, to avoid overtreatment of a substantial proportion of low risk patients in future trials, a better definition of risk factors is warranted.

ADVANCED STAGES

Polychemotherapy with eight courses of either MOPP or ABVD is considered as the treatment of choice for patients with advanced HD. Many study groups now prefer ABVD or MOPP/ABVD over MOPP because of reduced toxicity. The complete remission rate of this "gold standard" is about 75%, with freedom from treatment failure rates of 50% after 5 years. So far, several international multicentre trials have been unable to obtain superior results by replacing drugs from the MOPP/ABVD protocol. Since the treatment results of advanced stage HD are still unsatisfactory, the major aim of ongoing and future studies is to improve on these results. In retrospective analyses, outcome was correlated with dose intensity [9]. Thus, one possibility of improving treatment results in HD is to use intensified doses of effective cytostatic drugs.

There are two principal ways to enhance dose intensity: dose escalation of drugs at a constant time interval or application of standard doses over a shorter period of time. Mathematical models developed by Hasenclever and colleagues suggest that a moderate dose escalation of 30% may result in a potential benefit of 10% at 5 years. This was the rationale for the HD9 study of the GHSG in which the BEACOPP protocol (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) was introduced to test whether dose escalation for cyclophosphamide and etoposide supported by G-CSF can improve treatment results in advanced stages [10]. The results of the BEACOPP run-in trial had been extremely encouraging with an overall CR rate of 95% and a freedom from treatment failure of 92% after a median observation time of 30 months as reported by H. Tesch, Köln.

Application of standard doses over a shorter period of time is the rationale for the Stanford V regimen which is a 12 week short-term hybrid protocol. The drugs are applied in three cycles of 4 weeks each, followed by radiotherapy to sites of initial bulky disease. This treatment was well tolerated in 94 patients as reported by S. Horning (Stanford). With a median follow-up of 3 years, survival is 93% and freedom from progression is 89% [11]. This seems to indicate that the Stanford V regimen is effective in advanced stages. The lower

cumulative dose of alkylating agents might reduce the long term side-effects in terms of fertility. In addition, the reduction of radiation volume in this protocol might further decrease the risk from second malignancies and cardiopulmonary toxicity.

Another interesting new strategy in the treatment of patients with advanced HD is the sequential application of high doses of the putatively most effective single agents as performed by the Milan Cancer Institute. Their more recently proposed regimen consists of epirubicin, vincristine, prednisone, cyclophosphamide and etoposide. The drugs are applied at 14 day intervals followed by radiotherapy from day 118. G. Bonadonna for the Milan group reported 48 previously untreated patients with stages IIB–IV. The treatment was well tolerated and effective, resulting in 75% complete remissions after chemotherapy and 94% after radiotherapy.

The role of additional radiotherapy in the treatment of advanced stages was discussed during the meeting. The South-West Oncology Group (SWOG) randomised patients to receive either radiotherapy or nothing after three courses of MOPP/ABVD. The results were superior in the radiation arm. In the HD-3 trial of the GHSG, patients with complete response after three cycles of COPP/ABVD were randomised to receive either 20 Gy IF or one additional course COPP/ABVD. There was no significant difference between the two arms. In their ongoing H 89 trial, the GELA group compares two additional cycles of chemotherapy versus 30 Gy STNI plus 5 Gy IF after six courses of either ABVPP or MOPP/ABV.

Another very important workshop held during the symposium dealt with the question of early high-dose chemotherapy in HD. Existing preliminary data presented by A. Carella, Genoa, suggest a disease-free survival of 70–80% of patients in advanced stages offered high-dose chemotherapy after achieving a complete response upon initial MOPP/ABVD treatment. Based on these pilot data, a prospective randomised trial has been initiated. R. Fisher, Loyola University responded to the enthusiasm of using high-dose chemotherapy in large randomised trials with a word of caution. Since the population at high risk for failure to initial treatment still cannot be identified precisely, high-dose chemotherapy trials means an overtreatment for a substantial proportion of patients. Thus, careful choice of effective but not excessively toxic regimens is warranted, along with careful long-term follow-up for toxicity. The ultimate endpoint of these trials still remains the overall survival.

FUTURE STRATEGIES

New biological treatment strategies aimed at eliminating residual H-RS cells are being pursued. HD seems suitable for immunotherapy for several reasons: (1) H-RS cells express large numbers of cell surface markers such as CD25 and CD30 which are present only on a small minority of normal human cells; (2) The number of the malignant H-RS cells which need to be eliminated is small; (3) Compared to solid tumours, Hodgkin lymphomas are well vascularised suggesting an easier access of monoclonal antibodies (MAbs) or other immunoconjugates.

A. Engert, Köln, reported on a recently performed phase I trial with a construct consisting of a monoclonal antibody which was chemically linked to the toxin ricin-A chain. This immunotoxin (IT) termed RFT5.dgA targeted against the CD25 antigen had been selected on the basis of superior *in vitro* and *in vivo* potency in experimental models. 15 heavily pretreated patients with end-stage, refractory HD were included in this trial. The IT was administered i.v. over 4 h every other day for 7 days. Patients received one to four courses of IT at doses of 5, 10, 15 or 20 mg/m^2. Side-effects were related to the vasculary-leak-syndrome, i.e. decrease in serum albumin, oedema, weight gain, hypotension, tachycardia, myalgia and weakness. Responses included 2 partial response, 4 stable disease and 9 progressive disease. The maximal tolerated dose was reached at 15 mg/m^2. This study will be continued in phase II.

Another approach was introduced by F. Hartmann, Homburg, Germany. His group used the bispecific monoclonal antibody HRS-3/A9 with binding activity against the CD30 antigen and the CD16 surface molecule on NK-cells. Experimentally, HRS-3/A9 triggers the lysis of CD30-positive Hodgkin cells. First results of a dose escalation study in 11 patients with refractory HD were reported. Treatment consisted of a total of four infusions administered every 3–4 days. Doses up to 16 mg/m^2 were well tolerated. Toxicity was mild with fever and pain in affected lymph nodes in 2/11 patients. Allergic rash occurred in 1 patient. 25% of the patients developed human-anti-mouse antibodies. 7 patients were evaluable for response showing one partial response, two minor responses and one mixed response. The maximum tolerated dose has not been reached yet.

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