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WORKSHOP REPORT

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2. Report on the Workshop: "Clinical Consequences of Pathology and Prognostic Factors in Aggressive NHL"

Introduction

The IPI has been generally accepted as a prognostic factor system used for reporting clinical trials [1]. It is also used for defining risk groups as inclusion criteria for clinical trials. The IPI system has been confirmed in many independent investigations. With the increasing molecular understanding of the disease a large variety of other potentially relevant candidates for prognostic factors has been proposed. Many of these have a molecular background and seem to link to the genetic and kinetic heterogeneity of the disease. Furthermore the new histopathological classification system has promoted new histopathological entities [2].

This situation has raised questions among clinicians as well as trialist groups on the clinical consequences of prognostic factors and pathology.

The objective of this workshop was to provide answers to the following three leading questions:

(Q1): Which criteria should generally be requested in order to recommend splitting the population of aggressive NHL patients into groups with different treatment strategies?

(Q2): Should we allocate the following histopathological entitites into treatment protocols different than the standard chemotherapy treatments for DLBCL: T-cell lymphomas, immunoblastic variant of DLBCL, large mediastinal B-cell lymphoma, ALCL. Should we differentiate treatments according to biological factors (tumour growth velocity, elderly age)?

(Q3): Is there enough evidence and need now to define specific prognostic factors other than the IPI-criteria to be used in clinical trial protocols.

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Methodology

The workshop took place on September 23rd 2000 in Saarbrücken preceding the International Symposium on Biology and Treatment of Aggressive Lymphomas. The chairpersons requested specific contributions related to the above mentioned questions from a variety of authors and discussants. The contributors received specific questions in advance. These were accompanied by a discussion paper describing five theses on what should be considered when discussing therapeutic consequences of pathology and prognostic factors. The final version of this paper is included in these proceedings [3]. The workshop was attended by about 80 experts primarily from Austria, Canada, England, France, Italy, Germany, The Netherlands, Spain, Scandinavia, Switzerland, and the USA.

Question 1: Which criteria should generally be requested in order to recommend splitting the population of aggressive NHL patients into groups with different treatment strategies?

Drawing clinical consequences from pathology or prognostic factors from a clinical trial perspective inevitably implies to consider the segregation of patients into subgroups which are treated within different trials. The first round of discussion focussed on the question which criteria should be adopted to consider such a decision.

Markus Loeffler and Dirk Hasenclever discussed this question from a conceptual and biometrical point of view [3]. They argued that the scientific community should adopt a conservative attitude towards splitting patient populations between trial protocols.

Their main arguments were as follows:

(1) Prognostic factors for treatment outcome are neither necessary nor sufficient criteria for splitting patient populations. The main reason is that prognostic factors are generally determined independent of treatment strategies.
(2) A necessary criterion, however, is evidence for a strong subgroup dependent difference in treatment outcomes in comparative randomised trials. In statistical terms this is called a subgroup by treatment interaction. It implies that a clinical consequence of a prognostic factor should only be considered if there is clear evidence that a novel treatment principle has beneficial efficacy in this subgroup over standard treatment compared with other subgroups.
(3) An additional criterion is an acceptable toxicity/benefit trade off. This should be supported by analyses of prognostic factors for toxicity.

The major implication of these considerations is that we need to critically revise current strategies to draw clinical consequences. Most clinical researchers believe that prognostic factors themselves help to separate out cohorts of patients and disregard the interaction argument.

In this context one can distinguish two situations. Either a treatment can be considered as "specific" (i.e. qualitative) on the ground of insight into the biological mechanisms (e.g. specific antibodies; specific interference with intracellular signalling processes). Then prospective trials have to show that this specific treatment principle offers benefits over the standard in the specific subgroups. Or a treatment cannot be considered as "specific" in the above sense (like e.g. chemotherapies, radiotherapies). Then a working hypothesis has to specify why there should be a quantitative difference in responsiveness in some subgroups of the heterogeneous patient population. The relevant parameters to consider may be particular drugs, their dosage, the timing etc. Although prospective trials are also needed in this situation, there is a possibility to collect some evidence in favour of the hypothesis from existing clinical trial data by means of metaanalysis (see below).

A major problem with identification for treatment by subgroup interactions, however, is that statistical tests on interactions (i.e. differences of differences) require much larger case numbers than simple differences. Furthermore one needs to protect oneself against false positive findings due to multiple testing occurring in explorative searches for subgroups. As a prevention one should specify clear research hypotheses that a particular difference between two types of treatment should lead to observable differences in the outcomes between specific subgroups. Such predictions can then be tested in a special type of metaanalysis of randomised trials comparing the two types of treatments with regard to the prespecified subgroups. Such meta-analyses will be proposed below.

The discussion of the contribution by Loeffler and Hasenclever showed general agreement with the reluctant attitude towards splitting the patient populations. In particular the representatives from the large trial groups confirmed that they tend to maintain broad inclusion spectra in their trials largely avoiding setting up different trials for specific subgroups.

Subsequently, the workshop turned to discuss more specifically clinical situations.

Question 2: Clinical consequences for specific histopathological entitites

The workshop extensively discussed whether there is evidence to select non-standard treatments for the following four histopathological entitites.

(a) T-cell lymphomas versus B-cell lymphomas

In a seminal lecture Christian Gisselbrecht provided novel data from the GELA-group. In their series about 15% of all patients with aggressive NHL had T-cell lymphomas. The IPI-index was confirmed to be prognostic for these patients. Pooled comparisons show that B-cell lymphomas do generally better than T-cell lymphomas. However, when performing interaction tests, it was detected that no differences exist in the low IPI groups between B- versus T-cell lymphomas but about 20% differences in overall survival in the high IPI-groups. When looking into T-cell lymphomas more closely the GELA observes a favourable prognosis for ALCL+ T-cell lymphomas compared with ALCL- T-cell lymphomas and a significant interaction between anaplastic subtype and B- or T-cell lineage (non anaplastic T-cell lymphomas having the worst prognosis).

Dr. Kluin-Nelemans subsequently showed data from the EORTC 20901 trial suggesting that the ALCL- patients were performing better than patients with DLBCL. However, she did recommend to keep the patients in the general trials with adequate stratification. This opinion was supported by Julie Vose.

When discussing treatment options for T-cell lymphomas it became apparent that there is no evidence at present to treat T-cell lymphoma patients differently than the large majority of B-cell lymphomas. The general difference of prognosis between B- and T-cell lymphomas was confirmed by the SWOG. Furthermore, limited experience with high dose therapy was reported by Richard Fisher (SWOG), however, outcomes were so far not impressive. Christian Gisselbrecht reported that the GELA was considering a phase II study for T-cell lymphomas with intensified chemotherapy.

Taken together, there was a consensus that standard treatment of T-cell lymphomas is not different than standard treatment for all aggressive NHL. Other (more intensive?) treatments should only be given inside prospective randomised clinical trial protocols.

It was, however, mentioned by Christian Gisselbrecht that the novel antiCD20-antibody treatment for B-cell lymphomas may change the panorama in the future (Note: At the time of the meeting the GELA-results on CHOP±Rituximab where not yet available [4]). If the antibody treatment proves to be effective this may open different pathways for future developments of chemotherapy treatments in B- and T-cell lymphomas.
Hence the following consensus was apparent:

- The general prognosis of T-cell lymphomas is worse than that of B-cell lymphomas.
- There is at present no established or recommended treatment for T-cell lymphomas other than the standard treatments for aggressive NHL.
- Novel strategies should be investigated only in the setting of prospective randomised clinical trials.

(b) Immunoblastic versus centroblastic variant of DLBCL

Dr. Feller presented novel data from the German Study Group for High Grade NHL regarding the prognostic difference of the two variants of diffuse large B cell-lymphoma. Based on an interim analysis of the NHL-B-trial [5] a total of 418 specimen had been subjected to a central reference pathology review. Of these 70 cases were identified as immunoblastic and 348 as centroblastic. There were slight differences with regard to patient characteristics primarily regarding the IPI distribution. In (univariate) logrank tests marked differences in overall survival (SV, p=0.015) and time to treatment failure (TTTF, p=0.0017) were found. In the corresponding multivariate analysis adjusting for IPI the presence of the immunoblastic variant was associated with a moderate risk increase with respect to TTTF (RR=1.4, P=0.046) but no effect regarding overall survival could be revealed.

Two discussants contributed further data. Dr Brittinger reported data from a former German study using the COPBLAM-scheme which showed that the two variants were prognostic factors independent from the IPI . Christian Gisselbrecht presented an analysis of the GELA performed for the workshop where the prognosis of 1136 cases of the centroblastic variant were compared with 130 cases of the immunoblastic variant showing no independent prognostic relevance when adjusted for IPI.

Harald Stein annotated that the immunoblastic variant satisfies the criteria of a quantitative marker rather than of a distinct morphology. There was consensus among pathologists that better objective and reproducible criteria should be established to support the diagnosis.

Turning to clinical consequences no data had been provided on any treatment by subgroup interaction. Taken together there was unanimous consensus among all workshop participants that patients with the two variants should be treated in the same way and there was no reason to change treatment strategy for the immunoblastic variant.

(c) Large mediastinal B-cell lymphoma (LMBCL) versus DLBCL

Dr. Moeller made the point that according to his cytogenetic data, LMBCL is not a centroblastic lymphoma but rather satisfies criteria for a special type of extranodal lymphomas [6]. This would, however, have not direct implications with regard to treatment options.

No data sets comparing the prognosis of LMBCL and DLBCL were provided in the workshop. A retrospective analysis presented by Franco Cavalli was suggestive that time intensive chemotherapies like MACOP-B or sequential high dose treatment may reduce relapse rates somewhat, but data were partly confounded by a biased use of radiotherapy.

Pier-Luigi Zinzani analysed a series of 50 LMBCL-patients treated with MACOP-B and radiation. After chemotherapy 23% were in CR, after RX 78%. He also argued for performing a Gallium-SPECT scan to predict CR.

Regarding this level of evidence no discussion arose regarding changes of chemotherapy. However, a controversial discussion focussed on the role of radiation for LMBCL. Some experts shared the opinion that radiation should be included in a combined modality setting in stages of limited stage I and II disease. No majority opinion could be obtained on the role of radiation in advanced stage disease, where chemotherapy alone was considered an option.

(d) Anaplastic large cell lymphoma (ALCL)

Dr. Gascoyne discussed various issues of the pathology of ALCL-lymphomas which is descirbed in more detail in a separate paper in this issue [7]. His major conclusion was that it is necessary to collect more reliable data on this entity by a mandatory ALK-staining.

Considering the discussion reported in the paragraph on T-cell lymphomas there was no apparent argument for drawing clinical consequences at the present level of evidence. The general opinion was to treat these patients according to standard regimens.

Question 2: Clinical consequences of biological factors

The workshop then discussed whether particular biological features require clinical consequences. The two issues selected were the role of old age and of tumour growth kinetics.

(a) Clinical consequence of elderly age

Ralph Meyer presented a seminal talk on this issue [8]. The major conclusion is that full dose CHOP-chemotherapy is the standard treatment for all elderly patients without comorbidity.

This view is further supported by data from the NHL-B-trial of the German Study group for high grade Lymphoma as presented on the International Symposium by Michael Pfreundschuh. In this trial a cohort of patients aged 60 to 75 years was treated with either 6 cycles of 2 or 3 weekly CHOP or CHOP+Etoposide (CHOEP) [5]. Based on over 450 patients in this cohort an excellent compliance was achieved for patients with 2 weekly CHOP (supported by GCSF). More than 95% of all elderly patients not progressing during treatment received over 80% of the drugs planned. The interim analysis also suggests remarkable improvements of treatment outcomes in these intensified CHOP-variants. The German Study Group for high grade Lymphomas has decided to apply full dose 2 weekly CHOP with GCSF-support as standard treatment in the next trial generation for patients aged between 60 and 80 years started in July 2000.

(b) Clinical consequences of tumour growth velocity for the design of chemotherapies

Aggressive NHL is a mixture of diseases each of which is heterogeneous with regard to growth kinetics. A major source of heterogeneity lies in the tumour growth velocity. It is well known that tumours of one histopathological entity are not kinetically uniform but in some patients may grow within few weeks while in others it takes many months or years. Another source of heterogeneity is the sensitivity of the tumours to cytotoxic treatments. Both heterogeneities are difficult to quantify and we do not have good and reliable direct measurements on the status of tumour growth velocity or chemosensitivity at the time of deciding on the treatment. With regard to tumour growth velocity LDH or the IPI are generally considered as correlated surrogate parameters. With regard to chemosensitivity apoptosis parameters (eg p53 mutation) may provide some insight in the future.

In marked contrast to these underlying heterogeneities the usual chemotherapies applied to these patients (eg standard CHOP) are very uniform in dosing and timing. This discrepancy raises the obvious question whether and how one can design chemotherapies which better account for the kinetic heterogeneity.

To approach this objective Dirk Hasenclever and coworkers have presented a predictive model theory linking chemotherapy sensitivity and tumour growth velocity. The model is described in greater detail in a separate paper in this issue [9]. The model has three basic ingredients.

(1) On the basis of a meta-regression analysis of many comparative clinical trials the model achieved estimates of the relative weight of cytotoxic drugs in poly-chemotherpy regimens used in aggressive NHL. This permits to calculate the nominal weighted total dose for each regimen.

(2) To obtain an effective dose this nominal total dose needs to be corrected for the tumour regrowth in treatment intervals. The critical parameter is the ratio of the treatment interval and the tumour latency time. A large ratio implies that the effective dose of chemotherapy is reduced markedly over the nominal total dose.

(3) To predict the amount of long term tumour control achieved by this effective dose the model requires an estimate of the slope of the corresponding dose- response relationship.

A meta-regression analysis of 78 trials on aggressive NHL has permitted estimates of the drug weights, of the slope of the dose-response and of the median latency time. The analysis, however, also showed a remarkable degree of heterogeneity not explained. This was not surprising as the underlying assumption in this analysis was that all drug weights, the latency times and the slope of the dose response were homogenous over the entire population of aggressive NHL.

In the light of the above mentioned factors of hetereogeneity Dirk Hasenclever and coworkers investigated the possibility that a heterogeneity of tumour latency and chemosensitivity (i.e. differences in the slope of the dose-response) may be considered. The model in fact predicts that treatment with a shorter duration should be more effective in tumours with short latency times.

This idea generates the research hypothesis of a statistical interaction between chemotherapy treatments and tumour growth velocity. More specifically the conjecture originating from the model considerations is, that two chemotherapies with similar nominal weighted dose but different treatment durations should lead to similar tumour control in groups with slowly growing tumours while there should be marked benefits in subgroups with rapidly growing tumours.

Hasenclever et al provided a set of data from the literature and from the German Study Group of high grade Lymphoma that were clearly indicative for this conjecture with LDH being used as surrogate parameter for growth velocity [9].

Corinne Haioun provided related data from the GELA LNH 87-1 protocol. In this trial no overall survival difference was observed in a trial comparing the ACVBP-regimen and the m-BACOD-regimen on the basis of 670 patients. However, the interaction test was significant (p=0.02) indicating a better tumour control by the shorter ACVBP-protocol in the IPI 2,3 subgroups (RR=0.5).

Preliminary analyses of these data by the effective dose model suggest that the effects possibly indicate that more rapidly growing tumours may also have a larger chemosensitivity.

To perform a rigorous statistical analysis of this conjecture Hasenclever and Loeffler suggested to perform a metaanalysis of all randomised trials comparing chemotherapy regimens that differ in treatment durations and to investigate the interaction between these treatments and the surrogate markers for tumour growth velocities (IPI, LDH). Many trial groups agreed to participate in such an analysis during and after the workshop and preparations are presently going on to launch the project.

Question 3: New prognostic factors

The final issue discussed on the workshop was related to the question: Is there enough evidence and need now to define specific prognostic factors other than the IPI-criteria to be used in clinical trial protocols?

Emilio Montserrat provided a comprehensive overview over the field, which is described in detail in a separate paper in this issue [10]. Further contributions to this subject came from Dr Haioun, Dr Gilles-Salles and Margaret Shipp.

The general consensus was that the IPI represents the hallmark of prognostic factors for aggressive NHL and that no amendments should be made to this system at present.

On the other hand many experts have expressed the need to elaborate a novel prognostic factor system that is more based on biological principles. However, no consensus could be achieved yet on how to approach this goal. At least two directions became visible. Emilio Montserrat advocated for a differential approach using the IPI as a general basis and adding further factors X to account for specific features of each histopathological entity (e.g. DLBCL, T-cell lymphomas etc.). Maragret Shipp advocated to wait for the upcoming investigations on gene expression analyses. She presented own data on gene-profiling performed in 58 patients. Here a "lympho-chip" was produced with a selection of several genes which were segregating the survivors and non-survivors in the training data set. A confirmation of this interesting technique in an independent cohort of patients was, however, considered necessary.

To investigate the independent contribution of the various factors and the standardisation of the techniques to make these factors reliably measurable in large multi-center settings will require much more effort in the future. In particular comprehensive multivariate analyses will be required and broad international cooperation will be necessary to undertake this effort in parallel in several independent study groups.

References

1. Shipp M (1994) Prognostic factors in aggressive non-Hodgkin's lymphoma. Blood 93:1165–1173
2. Harris N et al. (1994) A revised European-American classification of lymphoid neoplasms. Blood 84:1361–1392
3. Hasenclever D, Loeffler M (2001) Five theses concerning the clinical consequences of pathology and prognostic factors. In: Schmits R, Truemper L, Pfreundschuh M (eds) Proceedings of the First International Symposium on Biology and Treatment of Aggressive Lymphomas (Suppl III) 80:B53–B55
4. Coiffier B et al. (2000, ASH) MABTHERA (Rituximab) plus CHOP is superior to CHOP alone in elderly patients with diffuse large B-cell lymphoma: Interim results of a randomized GELA trial, Blood 96, 223a (abstract 950)
5. Schmits R, Glass B, Truemper L, Pfreundschuh M et al (2001) Therapeutic strategies in adult NHL-patients: The trials of the German Study Group of high grade NHL. In: Schmits R, Truemper L, Pfreundschuh M (eds) Proceedings of the First International Symposium on Biology and Treatment of Aggressive Lymphomas (Suppl III) 80:B70–B76
6. Barth T, Leithäuser F, Moeller P (2001) Mediastinal B-cell lymphoma, a lymphoma type with several characteristics unique among diffuse large B-cell lymphomas. In: Schmits R, Truemper L, Pfreundschuh M (eds) Proceedings of the First International Symposium on Biology and Treatment of Aggressive Lymphomas (Suppl III) 80:B44–B48
7. Gascoyne RD (2001) Therapeutic consequences of pathology and prognostic factros in aggressive NHL-Analysis of ALCL. In: Schmits R, Truemper L, Pfreundschuh M (eds) Proceedings of the First International Symposium on Biology and Treatment of Aggressive Lymphomas (Suppl III) 80:B40–B43
8. Kouroukis CT, Meyer RM (2001) Treatment Sstrategies in elderly patients with aggressive histology NHL. In: Schmits R, Truemper L, Pfreundschuh M (eds) Proceedings of the First International Symposium on Biology and Treatment of Aggressive Lymphomas (Suppl III) 80:B79–B81
9. Hasenclever D, Brosteanu O, Gerike T, Loeffler M (2001) Modelling of chemotherapy: the effective dose approach. In: Schmits R, Truemper L, Pfreundschuh M (eds) Proceedings of the First International Symposium on Biology and Treatment of Aggressive Lymphomas (Suppl III) 80:B82–B87
10. Montserrat E (2001) Prognostic factors in aggressive lymphomas: the contribution of novel biological markers. In: Schmits R, Truemper L, Pfreundschuh M (eds) Proceedings of the First International Symposium on Biology and Treatment of Aggressive Lymphomas (Suppl III) 80:B37–B39