Therapeutic strategies for aggressive lymphomas

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General treatment strategies for aggressive lymphomas

The term "aggressive lymphomas" has been coined for a group of lymphomas classified according to the REAL (Revised European–American Lymphoma) classification that are characterised by a clinical course that is rapidly fatal if not treated successfully [1]. While there is no clinical grouping of lymphoma entities in the new WHO (World Health Organization) classification [2], which has evolved from the REAL classification [3] and is now widely accepted worldwide, the clinical groups of the REAL classification can be translated into and recovered from the WHO classification [2]. As can be seen from Table 1, aggressive lymphomas comprise the majority of the former intermediate–high grade and high grade lymphomas. While there is general consensus that the lymphoblastic lymphomas of both the T- and B-cell type should be treated according to aggressive treatment protocols used for the respective types of acute lymphocytic leukaemias, there is some debate as to whether Burkitt's lymphomas do indeed have a worse prognosis than the diffuse large B-cell lymphomas if treated and evaluated according to their risk profile [4] (see below).

The diagnosis of aggressive lymphoma is always an indication for a curative and hence intensive therapeutic approach. The adequate experience of the treating physician and the institution is a prerequisite for the consequent administration of such therapies and must guarantee the permanent availability of the necessary supportive care. Therefore, patients with aggressive lymphoma should only be treated in institutions that fulfil these criteria.

A curative therapeutic approach is indicated both in young and elderly patients, even though the rate of complete remissions decreases and the rate of relapses of patients with aggressive lymphoma increases with age, resulting in a lower cure rate (Fig. 1). Most of the worse prognoses of elderly patients are due to the fact that the number of negative prognostic factors increases with age. When adjusted for the number of risk factors according to the IPI (International Prognostic Index) [5], the differences in prognosis between pa-

Table 1

Classification of aggressive and very aggressive lymphomas according to the REAL [3] classification translated into the WHO classification [2]

B-cell lymphomas
Aggressive lymphomas
diffuse large cell B-lymphomas
Morphological variants:
– centroblastic
– immunoblastic
– T-cell or histiocyte-rich, large cell anaplastic B-lymphoma
Clinical subtypes:
– mediastinal large cell B-lymphomas
– intravascular large cell B-lymphoma
– primary body cavity lymphoma
Very aggressive lymphomas
Burkitt's Lymphoma
Morphological variants:
– Burkitt-like
Clinical subtypes:
– endemic form (EBV-associated)
– sporadic form
– immunodeficiency-associated
Precursor-B lymphoblastic lymphoma
T-cell lymphomas
Aggressive lymphomas
peripheral T-cell lymphoma, not otherwise specified
extranodal NK-cell / T-cell lymphoma of the nasal type
angioimmunoblastic T-cell lymphoma
T-cell leukaemia / lymphoma of the adult (HTLV-1 positive)
anaplastic large cell lymphoma of the T- and null-cell type
subcutaneous panniculitis-like T-cell lymphoma
T-cell lymphoma of the enteropathy type
Hepatosplenic γδT-cell lymphoma
Very aggressive lymphomas
Precursor-T lymphoblastic lymphoma

REAL, Revised European–American Lymphoma; WHO, World Health Organization; EBV, Epstein-Barr virus; HTLV-1, human T-cell leukaemia virus type 1.

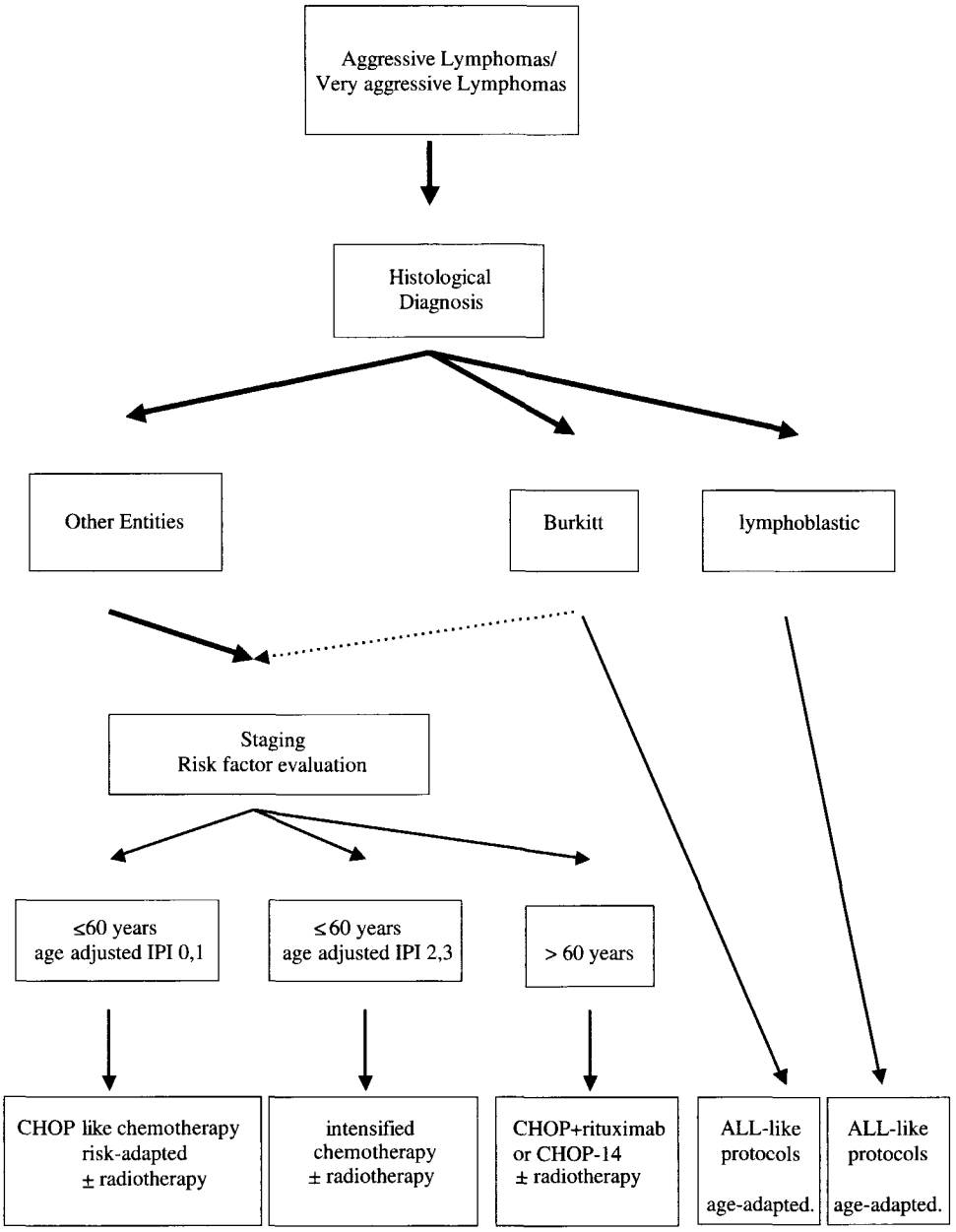

Fig. 1. Treatment strategies for patients with aggressive lymphomas. CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone. ALL: acute lymphoblastic leukaemia. IPI: International Prognostic Index.

tients ≤ 60 years and > 60 years of age is far less pronounced. A palliative approach is only justified if the results of the pre-treatment evaluation demonstrate relevant concomitant diseases that suggest an unacceptable degree of treatment-related morbidity or even mortality. Yet even in these patients, the decision as to whether they are eligible for a curative therapy or not should not be made until the end of a pre-phase treatment (see below).

Whenever possible, therapy of aggressive lymphoma should be given within prospective trials. This applies to all age and risk groups of patients, because the results obtained to date are by no means satisfactory and have to be improved under controlled conditions, a goal that can only be achieved within an acceptable time-frame by fast-recruiting large multicentre trials.

Besides age, other factors determine the prognosis of a patient with aggressive lymphoma. In a large meta-analysis of the International Non-Hodgkin's Lymphoma Prognostic Factors Project [5], the following pre-treatment parameters were identified as

Table 2
Age-adjusted IPI for patients ≤ 60 years and > 60 years of age [5]

Risk group	Proportion	No. of risk factors	CR rate*	5-year survival rate*
Low	22%/18%	0	92%/91%	83%/56%
Low-intermediate	32%/31%	1	78%/71%	69%/44%
High-intermediate	32%/33%	2	57%/56%	46%/37%
High	14%/16%	3	46%/36%	32%/21%

* Patients ≤ 60 years/patients > 60 years. CR, complete response.

independent negative prognostic factors:

- elevated serum lactate dehydrogenase (LDH)
- age over 60 years
- advanced stage (stages III and IV according to the Ann Arbor classification)
- poor performance state (> 1 according to the ECOG (Eastern Cooperative Oncology Group) scale)
- involvement of > 1 extra-nodal site of lymphoma involvement.

The number of risk factors determines the prognosis of a patient and hence the primary therapeutic strategy. Depending on the number of risk factors, patients are grouped into a low, low-intermediate, high-intermediate, and high risk group according to the IPI. CR rates and 5-year survival rate decrease from 87% and 73%, respectively, in the low-risk group to 44% and 26%, respectively, in the high-risk group. If an age-adjusted risk factor analysis is performed, the presence of only 1 risk factor is already relevant, and the presence of > 1 extra-nodal site of involvement is not a risk factor for young patients (Table 2).

The IPI risk group does not only determine the prognosis of a patients, it is also a major determinant for the primary therapeutic strategy in aggressive lymphomas. High-dose chemotherapy approaches appear to be justified only for young high-risk patients, because young low-risk patients have a fair prognosis with conventional chemotherapy and for elderly patients high-dose chemotherapy is associated with excessive toxicity, with the cut-off age for high-dose approaches usually being set between the age of 60 and 65 years. Therefore, usually three therapeutic groups of aggressive lymphomas are distinguished with respect to the therapeutic strategy to be followed:

1. young patients of the low and low–intermediate risk group;
2. young patients of the high–intermediate and high-risk group; and
3. elderly patients (> 60 or > 65 years of age, respectively).

A further separation of very old patients (> 70 or > 75 years, respectively) does not appear to be justified, because the response to therapy, tolerability of therapy and prognosis of these patients is not substantially different from that of patients 60 to 70 years of age, if concomitant diseases do not interfere with a consequent administration of therapy. The upper age limit for a conventional chemotherapy with curative intent is not defined by the chronological age of a patient, but rather by the higher likelihood of associated co-morbidity of elderly patients. Patients up to 70 years rarely have exclusion criteria for a curative therapeutic strategy; however patients > 70 years of age must undergo a careful evaluation to identify concomitant diseases that are pre-existent or might emerge under therapy.

About 10% of the aggressive lymphomas are T-cell lymphomas. T-cell lymphomas have a somewhat lower remission rate than B-cell lymphomas and a significantly higher relapse rate, resulting in a lower cure rate. However, to date, there are no specific strategies that hold promise to diminish or even compensate for the poorer prognosis of some histological subtypes of aggressive lymphomas. Approaches with a positive and/or differential effect on specific subgroups can only be identified if these subgroups are lumped together into large randomised trials comprising all aggressive lymphomas, because only such trials allow for a contrasting analysis of the respective subgroups and offer the chance to identify interactions between different treatment arms and a defined subtype of aggressive lymphomas. As long as such interactions have not been identified, separate trials for subtypes are not justified, because there would be no way to develop differential strategies based on such interactions. Therefore, with the exception of the B-cell specific anti-CD20 antibody, rituximab, the therapeutic strategies to be discussed in the following paragraphs apply to aggressive lymphomas of both B- and T-cell origins.

While the role of surgery in the treatment of aggressive lymphomas is limited to a diagnostic procedure, chemotherapy and radiotherapy represent the cornerstones of the treatment strategies of aggressive lymphomas, with immunotherapy gaining increasing importance.

Radiotherapy

Aggressive lymphomas are very radiosensitive: doses between 36 Gy and 45 Gy are sufficient for the elimination of the malignant clone. Nevertheless, the value of radiotherapy for the treatment of aggressive lymphomas is ill-defined. Its application as an additive measure to chemotherapy for bulky disease and extra-nodal involvement is mainly derived from retrospective analyses. The curative potential of radiotherapy as a single modality decreases with the age of the patient; in particular patients > 70 years can not be cured by radiotherapy alone [6], even in stages I and II. Therefore, radiotherapy as a single modality treatment for aggressive lymphomas is obsolete.

Combined chemo-radiotherapy

As with radiotherapy alone, available data supporting the combined use of radio- and chemotherapy is not convincing; in particular, the optimal number of chemotherapy cycles as well as the volume and dose of radiotherapy to be given within such a combined modality approach have not been defined. While an early analysis of a randomised oligo-centre trial had suggested that a combination of 4 cycles of chemotherapy with the CHOP regimen and an intensified involved-field radiotherapy (45 Gy) is superior to 8 cycles of CHOP, a follow-up of this study revealed crossing-over of the curves after 7 years [7]. The interpretation of this study had been difficult to start with due to the inclusion of a significant proportion of patients with follicular and MALT (marginal zone lymphomas of extranodal type) lymphomas. More importantly, a large and well-designed trial of the French GELA (Groupe d'Etude des Lymphomes de l'Adulte) [8] demonstrated the superiority of 3 cycles of the ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone) regimen (which would correspond roughly to 6 cycles of a CHOP-like regimen) over 3 cycles of CHOP combined with involved-field radiotherapy of 30 to 40 Gy in patients < 60 years of age without any risk factor according to IPI. The patients who received full-cycle chemotherapy had a better 5-year event-free as well as overall survival. Finally, another large trial of the GELA in patients > 60 years with no IPI risk factors showed that the addition of involved-field radiotherapy to 4 courses of CHOP resulted in a worse overall survival of patients > 70 years [9]. Therefore, the available data suggests that full-cycle chemotherapy is better than reduced-cycle chemotherapy plus radiotherapy even in good-prognosis aggressive lymphoma.

Consolidation radiotherapy as an additive measure after a full-cycle chemotherapy is common practice by several cooperative groups for initial "bulky disease". This recommendation is only supported by one small Mexican study with 88 patients, where the addition of radiotherapy to primary "bulky disease" led to a prolonged relapse-free and overall survival [10]. In the NHL-B trial of the DSHNHL, all patients with bulky disease received 36 Gy to this area; while relapses in the irradiated primarily bulky disease area were not more frequent than relapses in other primary sites of involvement, bulky disease emerged as an independent negative prognostic factor despite radiotherapy [11]. Similarly, there is no data supporting additional radiotherapy for lymph nodes with persisting enlargement after chemotherapy (so-called "iceberg" radiotherapy). A similar lack of supporting evidence applies to approaches employing additive radiotherapy to sites of extra-nodal involvement. However, > 1 site of extra-nodal involvement, which is an independent risk factor according to the IPI, did not evolve as a risk factor in the NHL–B2 trial [11]. However, whether this is due to the fact that most patients in that trial received radiotherapy to extra-nodal sites of involvement remains to be shown.

In summary, the role of any form of radiotherapy in the treatment of aggressive lymphomas is not based on evidence from prospective trials. It is therefore not astonishing that large cooperative groups like the GELA have eliminated radiotherapy from their therapeutic armamentarium. Any form of radiotherapy can only be justified for aggressive lymphomas in the context of a prospective clinical trial.

Chemotherapy

In general, the most pronounced toxicity of a polychemotherapy regimen is to be expected after the first course of chemotherapy (so-called "first cycle effect"). In this respect, it is of interest that the degree of side effects correlates with the pre-therapeutic risk score according to the number of prognostic risk factors according to IPI. Nevertheless, the practice of giving the first chemotherapy course at reduced doses to patients with a reduced performance status and/or increased age is obsolete, because it can result in a vicious circle: because the tumour load is not reduced to an appropriate degree within a short time, the performance status of the patient improves only slowly, and even the dose-reduced chemotherapy is likely to cause side effects, that in turn requires treatment delays or dose reductions, resulting eventually in an insufficient therapy. Instead of starting with a

dose-reduced first cycle of chemotherapy, patients in a bad performance status, at an older age or with a big tumour load should instead receive a pre-phase treatment, consisting of 100 mg prednisone orally (p.o.) per day for about one week which might be completed by a single injection of 1 mg vincristine intravenously (i.v.) on the first day. The experience of the DSHNHL shows that such a pre-phase treatment results in a significant improvement of the performance status and nearly all patients are then able to tolerate a fully dosed first chemotherapy course.

Standard chemotherapy regimen: The combination of cyclosphosphamide, doxorubicin, vincristine and prednisone, known as the CHOP regimen, was the break-through in the treatment of aggressive lymphomas more than 25 years ago [12]. The CHOP regimen proved for the first time that a significant proportion of patients with aggressive lymphomas even in advanced stages can achieve a complete remission (50–70%) or even cure (30–50%). The success of CHOP led many groups to develop and test intensified regimens for patients with aggressive lymphomas in non-randomised trials. Many of these so-called second or third generation regimens were based on model calculations by Goldie and Coldman and the dose intensity concept developed by Hryniuk and adopted for lymphomas by DeVita. With these regimens CR rates up to 90% and 5-year survival rates up to 85% were observed in phase II trials, success rates that were nearly twice as good as those achieved with CHOP. However, when these regimens were compared with CHOP in the large randomised Intergroup Trial with 1200 patients, the intensified m-BACOD, ProMACE–CytaBOM, and MACOP–B regimens were shown not to improve CR rates, event-free and overall survival in comparison to CHOP [13]; however, they were more toxic, with therapy-associated death rates up to 6% compared with 1% with CHOP. Since the ACVBP regimen, which is the standard chemotherapy combination used by the GELA, proved to be not superior to m–BACOD [14], CHOP given every three weeks (CHOP–21) was recognised as the standard chemotherapy for more than 25 years.

Number of chemotherapy cycles: The dose intensity concept has neglected the importance of the total dose of a chemotherapy regimen; this applies in particular to regimens of the third generation such as MACOP–B, COMLA or variants thereof. It might well be that a potential advantage of these regimens with their increased dose intensity was compromised by the reduced number of cycles and the consequent lower total dose compared with CHOP. The number of CHOP cycles administered in different trials varies between 4 and 9; in the original publication 3 cycles were given after obtaining a CR [12]. While there is common consensus that a prolonged consolidation or maintenance therapy is of no value, but only increases toxicity, the results of retrospective studies do not allow any conclusions with respect to the optimal number of CHOP cycles. Results from prospective randomised trials addressing this point are not available. Supportive evidence that an increased number of cycles might improve the outcome of patients with aggressive lymphomas is derived from a small randomised study [15], where the addition of two cycles to patients in complete remission after 6 cycles of a CHOP-like regimen had a better relapse-free and overall survival. Indirect support that 8 cycles of CHOP might be better than 6 cycles comes from the comparison of the patients who received 6 cycles of CHOP–21 according to the NHL–B2 trial of the DSHNHL [11] and 8 cycles of CHOP–21 according to the LNH 98.5 trial of the GELA [16]: even though the GELA patients had a worse risk profile, the event-free and overall survival curves of the CHOP–21 patients in the 2 trials are virtually superimposable. This suggests that the 8 cycles in the French trial (two more than in the German trial) compensated for the worse risk profile of the patients. To definitely answer the question of 6 vs. 8 cycles, the DSHNHL is currently addressing this question in the RICOVER–60 trial.

We start with a discussion of the treatment of the elderly, not only because they represent more than half of all newly diagnosed patients with aggressive lymphoma, but also because it is in this subgroup of patients that significant progress has been made for the first time since the introduction of the CHOP regimen, i.e. in more than 25 years. This progress was achieved by employing strategies that can be also pursued in young patients. While these strategies have yet to be shown to improve the outcome of young patients, they show the direction for the design of the respective trials in the young.

Patients > 60 years

Many modifications of the CHOP regimen with less intensity have come up with disappointing results. This applies to dose-reduced weekly applications of CHOP, as well as to dose-modified regimens, where the anthracycline, doxorubicin, was substituted by mitoxantrone. Other regimens, such as VNCOP–B and the very similar PMitCEBO–Regime of the BNLI have never been compared with standard CHOP.

With the availability of G–CSF (granulocyte colony stimulating factor) and GM–CSF (granulo-

cyte macrophage colony stimulating factor) in the 1990s, most groups used these growth factors for dose escalation. Well-designed dose-escalation studies, however, that used the level and duration of neutropenia as the comparator [17] demonstrated that the dose escalation that is possible using these growth factors is < 25%. Yet, when they are used for the reduction of the therapy-free interval between chemotherapy cycles, a 2-week regimen would represent a 50% increase in dose intensity compared with a 3-week regimen. After demonstrating the feasibility of a combination of etoposide (100 mg/m^2 d1 to d3) and CHOP (CHOEP) given every 2 weeks (CHOEP–14), the DSHNHL started 2 randomised trials that compared CHOP with and without etoposide given every three and two weeks in young low risk (NHL–B1 trial: 18 to 61 years, low LDH; NHL–B2 trial: all patients 61 to 75 years of age).

The NHL–B trial with more than 700 patients showed that the bi-weekly CHOP–14 regimen significantly improved complete remission rates ($P = 0.006$), event-free ($P = 0.01$) and overall survival ($P = 0.001$) over the classical CHOP–21 after a median time of observation of nearly 5 years [11]. Both low-risk and high-risk patients profited from the 2-weekly regimen, but the positive effect of interval reduction was most pronounced in patients with elevated LDH where the CR rate increased from 48% to 70%. The improvement in treatment outcome with CHOP–14 was achieved without increasing clinically relevant toxicities such as leucocytopenia, serious infections or therapy-associated deaths. In contrast, the double intensive CHOEP–14 was too toxic, resulting in frequent treatment delays and an increased therapy-associated death rate. Therefore, CHOP–14 is the chemotherapy regimen of choice for patients >60 years of age.

Similar improvements as those obtained with CHOP–14 have been reported by the GELA by adding the chimeric monoclonal anti-CD20 antibody, rituximab, to the classical CHOP–21 in patients 61 to 80 years of age in stages II to IV [16]. Compared with CHOP–21 alone, the combination of CHOP with rituximab improved the results to an extent similar to CHOP–14: CR rates were improved by 14%, the rates of progressions under therapy decreased from 22% to 9%. Event-free and overall survival of nearly 400 patients was improved by 19% and 13%, respectively, after a median time of observation of 2 years (Fig. 2).

Thus, two novel approaches have succeeded in improving results over the classical CHOP–21, both without increasing clinically relevant side effects (Fig. 3). Only a randomised trial can tell which of the two is superior and will become the accepted standard for elderly patients with aggressive lymphomas. Because rituximab improves the outcome of aggressive lymphomas which express bcl-2 in particular [18], while interval reduction is of the greatest benefit for lymphomas with high LDH, different patients might profit from the different strategies. Similarly, the combination of both approaches is not necessarily better than either one: since we now start with significantly better event-free and overall-survival curves than with CHOP–21, further improvement will be more difficult to demonstrate, and it will not be demonstrated apart from in an appropriate

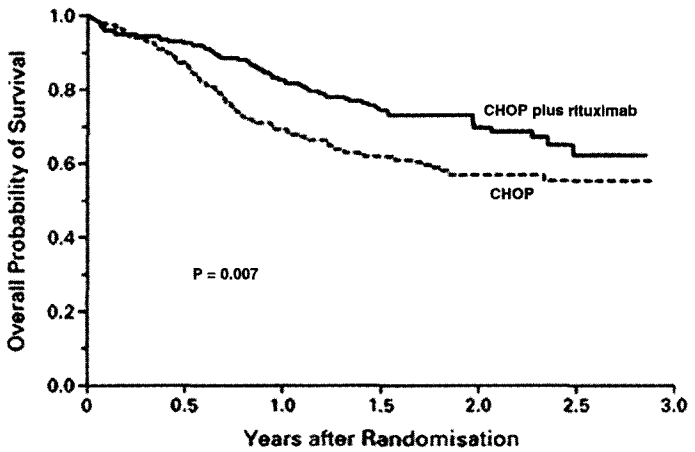

Fig. 2. Improvement of overall survival of elderly patients with diffuse large B-cell lymphomas treated with the CHOP regimen by the addition of the monoclonal anti-CD20 antibody rituximab (from Ref. [16]).

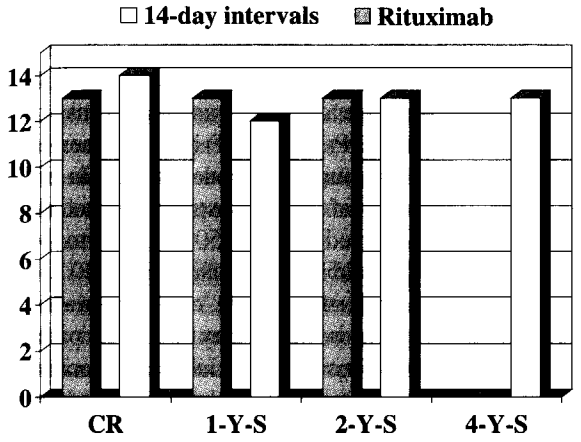

Fig. 3. Improvement of treatment results of elderly patients treated with CHOP achieved by the addition of the monoclonal anti-CD20 antibody or by "dose densification" (reduction of treatment intervals from CHOP–21 to CHOP–14). Note that the percentages of gain in complete remission (CR), 1-year and 2-year survival rates are similar.

randomised trial. Such a trial is the RICOVER–60 or 1999–1 trial of the DSHNHL which compares CHOP–14 with and without rituximab in patients 61 to 80 years of age. The GELA is currently comparing CHOP–21 with rituximab and CHOP–14 with rituximab in a randomised trial.

Young patients with a favourable risk profile

Due to the comparatively good outcome of young patients with a favourable risk profile (age-adjusted IPI 0 or 1) with CHOP–21, therapeutic improvements are more difficult to achieve and to demonstrate. Retrospective analyses of subgroups [19,20] could not demonstrate a benefit for this group of young low-risk patients by the use high-dose chemotherapy in the primary treatment, which has been largely abandoned for this group.

To test whether there is a window for dose-escalated or dose-densified regimens in young low-risk patients, NHL–B1 trial of the DSHNHL evaluated the role of interval reduction (CHOP–14) and/or the addition of etoposide (CHOEP–21, CHOEP–14) in young patients with normal pre-treatment LDH in a 2×2 factorial design. After a median follow-up of nearly 5 years, the etoposide-containing regimens CHOEP–21 and CHOEP–14 significantly improved CR rates and event-free survival in more than 750 patients [21]; overall survival, however, is not significantly different. This is most likely because half of the young patients with an event can be cured by salvage therapy using high-dose chemotherapy with stem cell support. The positive effect of etoposide was most pronounced in patients with 1 risk factor according to IPI, which was contributed nearly exclusively by advanced stages III/IV in this trial: in this subgroup event-free survival after 5 years increased from 46% to 70% ($P = 0.0009$) and overall survival from 72% to 85% ($P = 0.0097$).

In contrast to the addition of etoposide, interval reduction (CHOP–14, CHOEP–14) did not result in a significantly improved outcome of these young patients with elevated LDH, even though both CHOP–14 and the double intensive CHOEP–14 were well tolerated by the young patients and could be administered at a relative dose intensity of nearly 100%. Taking elevated LDH as a surrogate marker for fast growth, this is not surprising, because lymphomas with a slower growth rate can be expected to be less sensitive to the reduction of treatment intervals. However, when CHOEP–21, CHOP–14 and CHOEP–14 are each compared to the classical CHOP–21, it is only the double-intensive CHOEP–14 regimen that significantly improves not only CR rates ($P = 0.02$) and event-free survival ($P = 0.02$), but also overall survival ($P = 0.04$), the 3rd endpoint of the NHL–B1 trial. Therefore, while it is evident that CHOEP, i.e. CHOP plus an intermediate dose of etoposide, should be the new standard for young low-risk patients, the decision between CHOP–21 and CHOEP–14 is more difficult. Concluding from the results in the elderly, where the 2-week regimen was most beneficial for patients with elevated LDH, CHOEP–14 should be considered outside of clinical trials instead of CHOEP–14, for young low-risk patients that present with an elevated pre-treatment LDH.

The role of rituximab in the treatment of young low-risk patients with aggressive lymphoma remains to be determined; it is currently being evaluated in the MINT (Mabthera International Trial Group) trial, which compares CHOP or CHOP-like regimens with the identical regimens plus rituximab. Because nearly 50% are recruited by Germany and Sweden (where CHOEP is used as the new standard regimen) it will be very difficult to demonstrate a significant superiority by the addition of rituximab. The trial has recruited nearly 700 patients to date and should close after 820 patients by the end of 2003.

Young patients with an unfavourable risk profile

For this group of patients, the use of very aggressive therapy is justified and approaches with myeloablative high-dose therapy requiring stem-cell support are feasible with acceptable side effect. The superiority of high-dose chemotherapy compared to a conventionally dosed salvage therapy was demon-

strated for refractory and relapsed aggressive lymphomas in the PARMA study, where it was compared with DHAP, a combination of dexamethasone, cytosine arabinoside and cisplatin [22]. In contrast to relapsing and refractory aggressive lymphomas, the results of high-dose chemotherapy in the primary treatment of aggressive lymphomas are not convincing. The GELA LNH 87 study randomised patients in remission after 4 cycles of ACVBP into a consolidation with a sequential conventional chemotherapy or high-dose CBV (cyclophosphamide, carmustine and etoposide). No differences were observed between treatment arms [19]. However, a retrospective subgroup analysis revealed a benefit of the high-dose approach for patients of the high and high-intermediate risk groups with respect to relapse-free and overall survival [19]. Comparable results were reported by an Italian group [20] with respect to relapse-free, but not overall survival, while the NHL–A trial of the DSHNHL [23] as well as a HOVON [24] and an EORTC (European Organisation for Research and Treatment of Cancer) trial [25] did not observe any differences at all. Prospective trials that included only young patients of the high and high-intermediate risk groups failed to demonstrate an advantage of early high-dose chemotherapy [26] or even had to be terminated early because of inferiority of the high-dose arm [27]. Thus, there is only one small randomised trial that observed an advantage for the high-dose approach in event-free, but not in overall survival [28]. In summary, the recommendation of a consensus conference that convened in Lyon in 1997 is still valid: the administration of high-dose chemotherapy for the primary treatment of aggressive lymphomas is not justified outside of prospective clinical trials.

The Gianni approach differs from conventional high-dose chemotherapy strategies in several ways, among others by its use of high-dose methotrexate and the repeated application of single-drug chemotherapy courses close to the maximum tolerated dose; therefore, even if confirmed by the ongoing MISTRAL trial (which carries the risk of a potential bias due to the use of "iceberg" radiotherapy), it would remain a matter of debate whether such a superiority would be due to the use of high-dose chemotherapy or other components of the Gianni approach.

Two factors are discussed as being responsible for the failure of high-dose approaches to improve the outcome of young high-risk patients: first, the cytotoxic drugs used for the high-dose regimen are not the most efficacious for the treatment of aggressive lymphomas; and second, in many trials the high-dose chemotherapy was given after an abbreviated conventional chemotherapy; instead of an addition to a full-cycle chemotherapy, patients in the high-dose arm received high-dose chemotherapy as a substitute for 2 to 3 cycles of conventional chemotherapy.

Besides high-dose chemotherapy regimens, dose escalations of CHOP or CHOP-like regimens are being evaluated in young high-risk patients. In phase II trials the doses of cyclophosphamide could be more than quadrupled (from 750 mg/m^2 to 4000 mg/m^2) with doxorubicin escalated from 50 to 70 mg/m^2 [29]. While the results of such trials are difficult to interpret because they included patients from different risk groups, the increased incidence of secondary myelodysplastic syndromes and acute leukaemias in the latter study point to the potential risks of such dose escalations using haematopoietic growth factors, not to mention that the toxicity of such approaches is similar to the one observed after high-dose chemotherapy with stem cell support.

In a novel approach, the DSHNHL is trying to escalate cyclophosphamide, etoposide and doxorubicin, the most efficacious drugs for the treatment of aggressive lymphomas, and to integrate them into a high-dose concept which has been designated as Mega–CHOEP. Mega–CHOEP includes one cycle of dose-escalated conventional CHOEP followed by 3 cycles of the myeloablative Mega–CHOEP with stem cell support to be repeated in 21-day intervals. Results of phase II trials with Mega–CHOEP have been encouraging and show no increased risk of secondary myelodysplasia or AML [30]. In the 2002–1 trial of the DSHNHL the Mega–CHOEP concept is compared with 8 cycles of CHOEP–14, both with and without rituximab.

Formally, CHOP–21 is still the standard chemotherapy regimen for young high-risk patients because neither interval reduction nor rituximab have been tested in this population. However, in light of the NHL–B2 and the LNH 98.5 results that showed the superiority of reducing treatment intervals from 3 to 2 weeks and the beneficial effect of rituximab in the elderly, respectively, randomising young high-risk patients to CHOP–21 is difficult and probably no longer practicable. Because there are no generally accepted standards for the treatment of these patients, young high-risk patients should only be treated within large prospective randomised trials. The SAKK compares the "Gianni Approach" with CHOP–21 in the MISTRAL trial; the DSHNHL compares 4 cycles of Mega–CHOEP (of which 3 are given with stem cell support) with 8 cycles of CHOEP–14. For the few young patients with a high-risk profile who do not qualify for such trials, 4 cycles of ACVBP or 8 cycles of CHOEP–14 might be justified.

Experimental approaches

Encouraging reports that the resistance of aggressive lymphomas to cytotoxic drugs could be reversed by the use of drugs that inhibit the efflux of cytotoxic drugs from the neoplastic cells could not be confirmed as was the case with the continuous infusion regimens.

As discussed above, the chimeric mouse/human monoclonal anti-CD20 antibody rituximab is currently being evaluated for younger patients and in combinations with chemotherapy regimens other than 2-weekly CHOP. The pan-leucocyte anti-CD52 antibody, CAMPATH–1, is undergoing early clinical testing in particular for T-cell lymphomas, as are several immunotoxins, i.e. conjugates of antibodies with toxic moieties, such as ricin or saponin. Radiolabelled antibodies with specificity for the B-cell-associated antigens, CD19, CD20 and CD22, which showed higher response rates than their unlabelled counterparts in follicular lymphomas are under clinical investigation as a single conventionally dosed modality and in the high-dose setting requiring stem cell support for aggressive lymphomas. In follicular lymphomas, the radiolabelled antibodies showed a higher response rate and in some cases induced responses in patients refractory to the native antibody. However, in contrast to unlabelled antibodies, the combination of radiolabelled antibodies with chemotherapy will be probably be limited by the additive myelotoxic effects and thus will narrow the therapeutic window where they can be successfully employed for aggressive lymphomas [31].

Strategies of active immunotherapy, in particular the development of lymphoma vaccines, have so far been limited to the individually specific clonal idiotype of B-cell lymphomas. Despite their expensive production, they have proved successful in indolent lymphomas [31]. Specific antigens that are shared by a considerable proportion of malignant lymphomas and might therefore serve as targets for a more broadly applicable vaccine have not been identified to date, with the single exception of HOM–TES–14/SCP–1, which is expressed by two thirds of T-cell lymphomas [32]. Another interesting approach is the use of anti-sense oligonucleotides against bcl-2 [33]. However, both anti-sense and vaccine strategies can be expected to be more efficacious in indolent than in aggressive lymphomas, where their primary role might be in combination with chemotherapy and/or for the treatment of minimal residual disease and the prevention of relapses.

References

1 Hiddemann W, Longo DL, Coiffier B, Fisher RI, Cabanillas F, Cavalli F, et al. Lymphoma classification — the gap between biology and clinical management is closing. Blood 1996, 88: 4085–4089.

2 Jaffe ES, Harris NL, Vardiman J, Stein H. Pathology and genetics: neoplasms of the hematopoietic and lymphoid tissues. In: Kleihues P, Sobin LH, editors. World Health Organization Classification of Tumours. Lyon: IARC Press, 2001.

3 Harris NL, Jaffe ES, Stein H, Banks PM, Chan JK, Cleary ML, et al. A revised European–American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood 1994, 84: 1361–1392.

4 Todeschini G, Tecchio C, Degani D, Meneghini V, Marradi P, Balter R, et al. Eighty-one percent event-free survival in advanced Burkitt's lymphoma/leukemia: no differences in outcome between pediatric and adult patients treated with the same intensive pediatric protocol. Ann Oncol 1997, 8 (suppl 1): 77–81.

5 The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med 1993, 329: 987–994.

6 Vaughan-Hudson B, Vaughan-Hudson G, MacLennan KA, Anderson L, Linch DC. Clinical stage 1 non-Hodgkin's lymphoma: long-term follow-up of patients treated by the British National Lymphoma Investigation with radiotherapy alone as initial therapy. Br J Cancer 1994, 69: 1088–1093.

7 Miller TP, LeBlanc M, Spier C, Chase E, Fisher RI. CHOP alone compared to CHOP plus radiotherapy for early stage aggressive non-Hodgkin's lymphomas: Update of the Sotuhwest Oncology Gourp randomized trial. Blood 2001, 98: 724a.

8 Reyes F, Lepage E, Munck JN, Morel P, Coiffier B, Lederlin P, et al. Superiority of chemotherapy alone with the ACVBP regimen over treatment with three cycles of CHOP plus radiotherapy in low-risk localized aggressive lymphoma: The LNH93-1 GELA study. Blood 2003, 100: 93a (Abstract #343).

9 Fillet G, Bonnet C, Mounier N, Thieblement C, Ferme C, Quesnez B, et al. Radiotherapy is unnecessary in elderly patients with localized aggressive non-Hodgkin's lymphoma: results of the GELA LNH 93-4 study. Blood 2002, 100: 92a.

10 Aviles A, Delgado S, Nambo MJ, Alatriste S, Diaz-Maqueo JC. Adjuvant radiotherapy to sites of previous bulky disease in patients stage IV diffuse large cell lymphoma. Int J Radiat Oncol Biol Phys 1994, 30: 799–803.

11 Pfreundschuh M, Trümper L, Schmits R, Klöss M, Schmitz N, Glass B, et al. 2-weekly vs. 3-weekly CHOP with and without etoposide for patients > 60 years of age with aggressive non-Hodgkin's lymphoma: results of the completed NHL-B-2 trial of the DSHNHL. Blood 2002, 100: 774a.

12 McKelvey EM, Gottlieb JA, Wilson HE, Haut A, Talley RW, Stephens R, et al. Hydroxyldaunomycin (Adriamycin) combination chemotherapy in malignant lymphoma. Cancer 1976, 38: 1484–1493.

13 Fisher RI, Gaynor ER, Dahlberg S, Oken MM, Grogan TM, Mize EM, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. N Engl J Med 1993, 328: 1002–1006.

14 Tilly H, Mounier N, Lederlin P, Briere J, Dupriez B, Sebban C, et al. Randomized comparison of ACVBP and m-BACOD in the treatment of patients with low-risk aggressive lymphoma: the LNH87-1 study. Groupe d'Etudes des Lymphomes de l'Adulte. J Clin Oncol 2000, 18: 1309–1315.

15 Aviles A, Huerta J, Zepeda G, Guzman R, Diaz-Maqueo J. The role of maintenance therapy in the treatment of large-cell non-Hodgkin's lymphoma. Acta Oncol 1991, 30: 959–962.
16 Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 2002, 346: 235–242.
17 Pfreundschuh M, Hasenclever D, Loeffler M, Ehninger G, Schmitz N, Kirchner H, et al. Dose escalation of cytotoxic drugs using haematopoietic growth factors: a randomized trial to determine the magnitude of increase provided by GM–CSF. Ann Oncol 2001, 12: 471–477.
18 Mounier N, Briere J, Gisselbrecht C, Emile JF, Lederlin P, Sebban C, et al. Rituximab plus CHOP (R-CHOP) overcomes *bcl*-2-associated resistance to chemotherapy in elderly patients with diffuse large B-cell lymphoma (DLBCL). Blood 2003, 101: 4279–4284.
19 Haioun C, Lepage E, Gisselbrecht C, Salles G, Coiffier B, Brice P, et al. Survival benefit of high-dose therapy in poor-risk aggressive non-Hodgkin's lymphoma: final analysis of the prospective LNH87-2 protocol — a Groupe d'Etude des Lymphomes de l'Adulte study. J Clin Oncol 2000, 18: 3025–3030.
20 Santini G, Salvagno L, Leoni P, Chisesi T, De Souza C, Sertoli MR, et al. VACOP-B versus VACOP-B plus autologous bone marrow transplantation for advanced diffuse non-Hodgkin's lymphoma: results of a prospective randomized trial by the non-Hodgkin's Lymphoma Cooperative Study Group. J Clin Oncol 1998, 16: 2796–2802.
21 Pfreundschuh M, Trümper L, Schmits R, Klöss M, Schmitz N, Glass B, et al. 2-weekly vs. 3-weekly CHOP with and without etoposide in young patients with low risk (low LDH) aggressive non-Hodgkin's lymphoma: Results of the completed NHL-B-1 trial of the DSHNHL. Blood 2002, 100: 92a.
22 Philip T, Guglielmi C, Hagenbeek A, Somers R, Van der Lelie H, Bron D, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med 1995, 333: 1540–1545.
23 Kaiser U, Uebelacker I, Abel U, Birkmann J, Trumper L, Schmalenberg H, et al. Randomized study to evaluate the use of high-dose therapy as part of primary treatment for "aggressive" lymphoma. J Clin Oncol 2002, 20: 4413–4419.
24 Verdonck LF, van Putten WL, Hagenbeek A, Schouten HC, Sonneveld P, van Imhoff GW, et al. Comparison of CHOP chemotherapy with autologous bone marrow transplantation for slowly responding patients with aggressive non-Hodgkin's lymphoma. N Engl J Med 1995, 332: 1045–1051.
25 Kluin-Nelemans HC, Zagonel V, Anastasopoulou A, Bron D, Roozendaal KJ, Noordijk EM, et al. Standard chemotherapy with or without high-dose chemotherapy for aggressive non-Hodgkin's lymphoma: randomized phase III EORTC study. J Natl Cancer Inst 2001, 93: 22–30.
26 Martelli M, Gherlinzoni F, De Renzo A, Zinzani PL, De Vivo A, Cantonetti M, et al. Early autologous stem-cell transplantation versus conventional chemotherapy as front-line therapy in high-risk, aggressive non- Hodgkin's lymphoma: an Italian multicenter randomized trial. J Clin Oncol 2003, 21: 1255–1262.
27 Gisselbrecht C, Lepage E, Molina T, Quesnel B, Fillet G, Lederlin P, et al. Shortened first-line high-dose chemotherapy for patients with poor-prognosis aggressive lymphoma. J Clin Oncol 2002, 20: 2472–2479.
28 Gianni AM, Bregni M, Siena S, Brambilla C, Di Nicola M, Lombardi F, et al. High-dose chemotherapy and autologous bone marrow transplantation compared with MACOP-B in aggressive B-cell lymphoma. N Engl J Med 1997, 336: 1290–1297.
29 Shipp MA, Neuberg D, Janicek M, Canellos GP, Shulman LN. High-dose CHOP as initial therapy for patients with poor-prognosis aggressive non-Hodgkin's lymphoma: a dose-finding pilot study. J Clin Oncol 1995, 13: 2916–2923.
30 Glass B, Klöss MBW, Engert A, Trümper L, Bentz M, Loeffler M, et al. Primary treatment of aggressive non-Hodgkin's lymphoma by dose-escalated CHOP + etoposide followed by repeated stem cell transplantation: Mega-CHOEP, a phase I/II study of the German High Grade NHL Study Group. Proc ASCO 2000, 20: 289 a (abstract # 1154).
31 Press OW, Leonard JP, Coiffier B, Levy R, Timmerman J. Immunotherapy of non-Hodgkin's lymphomas. Hematology (Am Soc Hematol Educ Program) 2001, 221–240.
32 Xie X, Wacker HH, Huang S, Regitz E, Preuss KD, Romeike B, et al. Differential expression of cancer testis genes in histological subtypes of non-Hodgkin's lymphomas. Clin Cancer Res 2003, 9: 167–173.
33 Waters JS, Webb A, Cunningham D, Clarke PA, Raynaud F, di Stefano F, et al. Phase I clinical and pharmacokinetic study of bcl-2 antisense oligonucleotide therapy in patients with non-Hodgkin's lymphoma. J Clin Oncol 2000, 18: 1812–1823.