
Original article

The treatment of pediatric lymphomas: Paradigms to plagiarize?

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Summary

The excellent results in pediatric lymphomas presented at the Sixth International Conference on Malignant Lymphoma in Lugano encompass several emerging themes and provide paradigms which it may be possible to extrapolate to at least some adult lymphomas. In pediatric Hodgkin's disease, there is mounting evidence that radiation adds nothing except toxicity to effective chemotherapy regimens, with the possible exception that patients with bulky disease, particularly in the mediastinum, may benefit from involved-field radiation. This is of particular importance in view of the recently recognized high rate of late-occurring second solid tumors and cardiac infarction, largely referable to radiotherapy. It is likely that there will be greater efforts to eliminate radiation from treatment protocols wherever possible. In pediatric non-Hodgkin's lymphomas, the intensive regimens used by several cooperative groups in Europe and the United States have resulted in very high event-free survival rates—90% in B-cell lymphomas, and only slightly lower in T-cell lymphomas. These results stand in striking contrast to those obtained in adults with the same diseases, except those treated with the same treatment protocols, who appear to have a similar prognosis. Finally, progress in the characterization of the molecular abnormalities and viral association of pediatric lymphomas is leading to new approaches to diagnosis and the detection of minimal residual disease, as well as to the development of targeted treatment approaches.

Key words: childhood, diagnosis, lymphomas, targeted therapy, treatment

Introduction

Pediatric non-Hodgkin's lymphomas (pNHLs) represent a small percentage, perhaps 3%, of all NHLs in the industrial nations, but they have played a disproportionately important role as models for understanding the pathogenetic mechanisms and treatment of lymphoid neoplasia. The figure of 3% is misrepresentative in other ways: children constitute a much higher fraction of the populations of developing countries and a correspondingly higher fraction of lymphomas in these countries, which account for more than 90% of the world's people and 90% of global population growth. Leukemias and lymphomas are particularly important childhood neoplasms—they constitute 40%–70% of childhood cancers in all world regions. In contrast to the industrial nations, lymphomas often account for a higher proportion of lymphoid neoplasms in developing countries, e.g., Burkitt's lymphoma comprises 50% of all pediatric malignancies in equatorial Africa [1]. Fortunately, the lymphoid neoplasms are also among the most readily curable of disseminated cancers. In the 1960s, Burkitt in Uganda and Clifford in Kenya, in collaboration with North American oncologists, notably Burchenal, had already reported cures from chemotherapy alone—reports that must have inspired the pioneer chemotherapists to greater efforts [2, 3]. This early foundation has been effectively built upon, as was gratifyingly evident from this meeting, in which mature studies demonstrating that approximately 90% of pediatric B-cell lymphomas can be cured were presented by cooperative groups from several countries.

Pediatric oncologists, faced with designing chemotherapy regimens for pNHL have always enjoyed several advantages compared to their adult oncologist colleagues. They do not face the significant comorbidities often present in older adults, nor has there been such pressure to design regimens suitable for outpatient delivery—the relatively small number of pNHLs weighing heavily here. These factors, coupled to the much greater number of potential years of life saved in children, probably account, at least in part, for the apparently greater readiness with which pediatric oncologists have embarked upon very intensive therapies requiring a great deal of supportive care and lengthy hospital stays. The success of these approaches contrasts with the lack of progress in the treatment of adult NHLs. Some of the success achieved in pNHL is doubtless attributable to the biology of pNHL—the spectrum of pediatric lymphomas is much narrower than that of adult lymphomas, and all have high growth fractions. For example, lymphomas characterized by primary defects in apoptotic function and very low growth fractions, for which a clear demonstration of cure (at least when widely disseminated) has yet to be provided, are common in adults, but exceedingly rare in children. However, even if comparisons are, appropriately, restricted to high growth fraction NHLs, or even to lymphomas encompassed by the Working Formulation definition of high-grade lymphomas, the results with the regimens used in pNHL remain superior.

Interestingly, a comparison of regimens presently used
for pediatric lymphomas with those used for high growth-fraction adult lymphomas demonstrates the much greater planned (and without doubt, received) dose intensity of pediatric regimens (Table 1). Renewed interest in much more intensive regimens in adults has been stimulated, not surprisingly, by the recent demonstration that the newer protocols for adult 'diffuse aggressive lymphomas', for some years believed to result in significantly improved survival rates compared to earlier regimens, have no advantages over the venerable CHOP combination [4]. In contrast to the approaches to pediatric lymphomas, however, and possibly fostered by a sense of desperation, a gradual conviction that autologous bone marrow transplantation (ABMT) may be essential to the successful therapy of high growth-fraction lymphomas appears to be sweeping the world of adult lymphoma specialists (if the mood in Lugano was anything to judge by) – in spite of the fact that a clear demonstration of superiority over a conventional drug combination (DHAP) has only been provided in the context of a subgroup of patients with relapsed NHL. Even this may reflect the inadequacy of present conventional therapy rather than the success of ABMT. The excellent treatment results in pNHL (vide infra) raise the possibility that similar approaches may be effective in at least some adult NHLs with high growth fractions, although it is important to recognize the considerable biological differences among these lymphomas, and the possibility that not all biological subtypes may benefit from the same therapy.

Consideration of the late consequences of cancer treatment is of much greater importance in young persons than in older individuals and increases in importance in parallel to the fraction of patients curable with present therapy. Thus, it is appropriate that in the childhood lymphomas, greater emphasis is placed on studies directed toward minimization of late effects without compromising the excellent results being achieved. In particular, the effects of radiation on bone and soft tissue growth have been a powerful incentive to reduce the irradiated volumes or total dose of radiation, or even to eliminate radiotherapy completely from the primary treatment of children with lymphomas – even in patients with Hodgkin's disease, in which radiation has been a mainstay, indeed, the primary therapeutic modality for the greater part of this century. The recent disconcerting observations of high cumulative risk for second malignancies in patients treated for Hodgkin's disease (e.g., 28% at 25 years in the Netherlands study reported at the Lugano conference) [5–8], and the high risk of death from causes other than Hodgkin's disease, usually second malignancies and cardiovascular disease, in the Stanford series of 2475 patients treated between 1962 and 1995 (50% at 30 years), are sobering figures indeed [6]. Second solid tumors and cardiovascular disease appear to be primarily due to radiation, providing additional reasons to at least minimize the use of radiotherapy, and to eliminate it wherever possible.

The successes achieved in the treatment of pediatric lymphomas do not constitute grounds for complacency. Quite apart from the late effects, successful therapy

### Table 1. Comparison of dose/dose intensity in treatment regimens used in diffuse aggressive lymphomas (intermediate and high grade) in adults and children.

<table>
<thead>
<tr>
<th>Drug regimen</th>
<th>Dose/dose intensity of CTX</th>
<th>Dose/dose intensity of ADR</th>
<th>Dose/dose intensity of VCR</th>
<th>Dose/dose intensity of MTX</th>
<th>Dose/dose intensity of VP16</th>
<th>Dose/dose intensity of Ara-C</th>
<th>Other drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHOP</td>
<td>750 mg/m²</td>
<td>50 mg/m²</td>
<td>1.4 mg/m²</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Prednisone</td>
</tr>
<tr>
<td>m-BACOD</td>
<td>250 mg/m²</td>
<td>18 mg/m²</td>
<td>0.46 mg/m²</td>
<td>200 mg/m²</td>
<td>120 mg/m²</td>
<td>300 mg/m²</td>
<td>Dexamethasone</td>
</tr>
<tr>
<td>ProMAC-Cytob</td>
<td>650 mg/m²</td>
<td>25 mg/m²</td>
<td>1.4 mg/m²</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Prednisone</td>
</tr>
<tr>
<td>MACOP-B</td>
<td>217 mg/m²</td>
<td>8.3 mg/m²</td>
<td>0.46 mg/m²</td>
<td>400 mg/m²</td>
<td>None</td>
<td>None</td>
<td>Prednisone</td>
</tr>
<tr>
<td>84-30</td>
<td>125 mg/m²</td>
<td>25 mg/m²</td>
<td>0.7 mg/m²</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Prednisone</td>
</tr>
<tr>
<td>Vanderbilt</td>
<td>333 mg/m²</td>
<td>13 mg/m²</td>
<td>0.7 mg/m²</td>
<td>330 mg/m²</td>
<td>100 mg/m²</td>
<td>165 mg/m²</td>
<td>Bleomycin</td>
</tr>
<tr>
<td>BFM 86</td>
<td>1000 mg/m²</td>
<td>30 mg/m²</td>
<td>1.4 mg/m²</td>
<td>300 mg/m²</td>
<td>500 mg/m²</td>
<td>1200 mg/m²</td>
<td>Dexamethasone</td>
</tr>
<tr>
<td>SFOP LMB89</td>
<td>750 mg/m²</td>
<td>22 mg/m²</td>
<td>0.35 mg/m²</td>
<td>300 mg/m²</td>
<td>300 mg/m²</td>
<td>None</td>
<td>Prednisone</td>
</tr>
<tr>
<td>CODOX-M</td>
<td>1500 mg/m²</td>
<td>60 mg/m²</td>
<td>2 mg/m²</td>
<td>8000 mg/m²</td>
<td>8000 mg/m²</td>
<td>9000 mg/m²</td>
<td>Prednisone</td>
</tr>
<tr>
<td>IVAC</td>
<td>533 mg/m²</td>
<td>13 mg/m²</td>
<td>0.93 mg/m²</td>
<td>2240 mg/m²</td>
<td>300 mg/m²</td>
<td>2666 mg/m²</td>
<td>Ifosfamide</td>
</tr>
</tbody>
</table>

MTX in MACOP-B is given on days 8, 36, and 64.
Dose intensity is expressed as planned dose intensity.
Dose intensities are calculated as mgs per m² per week for cycles in which the drug is included at the highest dose.
Doses for SFOP, LMB89, and BFM 86 are given for the highest risk groups.
When a drug is given daily for 2 or more days, the total dose is given.
BFM 86 uses VM26 (teniposide) rather than VP16 (etoposide) except for patients with B-ALL. The dose of teniposide is given.
requires the use of highly toxic chemotherapy with acute potentially life-threatening effects. Clearly, the reduction of risk requires that all patients be treated with as little therapy as possible, but reduction in therapy must be performed judiciously in order to minimize the risk that survival rates will be correspondingly reduced. This requires, in the first place, a greater degree of individualization of present therapy (starting with improved definition of risk groups), and in the second, the development of novel therapeutic approaches with specificity for the malignant cell. The possibility of using biological markers to improve the definition of risk groups (and, indeed, to improve diagnostic accuracy [9, 10]) is being intensively explored, and was represented at the Lugano meeting by an examination of the prognostic significance of p53 expression in small noncleaved-cell lymphomas [9]. A different approach to the minimization of therapy is to characterize the response to therapy as precisely as possible and to modify treatment according to the rate of response. Ultimately, it may prove possible to govern at least the length of treatment by the response achieved to early therapy cycles. To this end, there has been considerable investment in the development of techniques (usually based on the polymerase chain assay, PCR) to accurately detect minimal disease states [10]. Finally, there are grounds to believe that the precise targeting of treatment will eventually be possible – preclinical models of therapeutic approaches based on molecular abnormalities or the presence of viral sequences in tumor cells are proliferating, and two were presented in Lugano [9].

**Hodgkin's disease**

The risk of developing a second solid tumor after Hodgkin's disease, unlike that of secondary leukemia, which appears to flatten off 10 years or so after completion of therapy, is small prior to 12–15 years, but thereafter continues to increase with age [7, 8]. Depending upon the age at diagnosis and the treatment regimen employed, the cumulative risk of breast cancer, for example, approaches 35% by age 40 [7]. Females treated in adolescence are at particularly high risk to develop breast cancer, the incidence ratio in one study, for example, being 75%. The risk of thyroid cancer is also high [7, 8]. Whereas leukemias and lymphomas appear to be a consequence of alkylating-agent therapy (the risk of both rising with increased exposure to alkylating agents), the increased risk of developing a solid tumor seems to be primarily a consequence of radiation. Nearly all solid tumors occur within a radiation field, and patients who develop breast cancer, for example, have received, on average, twice as much radiation as patients who do not [7].

These findings, in addition to the high incidence of nonmalignant complications related to radiation therapy, such as thyroid dysfunction, pulmonary toxicity, and impaired bone and soft tissue growth, provide a powerful stimulus to reduce the dose of radiation used in the treatment of children with Hodgkin's disease, even early-stage Hodgkin's disease. Indeed, since the majority of children treated today receive combined modality therapy, and radiation doses are usually less than 25 Gy, one must question whether radiation adds any therapeutic benefit to treatment (these doses, if radiation were used alone, would be considered inadequate to sterilize Hodgkin's disease in the radiated area). More than 25 years ago, Ugandan children with Hodgkin's disease were being treated with MOPP chemotherapy alone [12], but until recently, little interest has been shown in the possibility that radiation may add minimal therapeutic benefit to adequate chemotherapy in patients with early-stage Hodgkin's disease [13–18]. Two presentations at the Lugano conference addressed this issue. One was a Pediatric Oncology Group (POG) study of children with stages I to IIIA (pathologically staged) Hodgkin's disease, which was begun 10 years ago [19]. One hundred eighty-six patients aged 2 to 22 years were treated with two cycles of MOPP/ABVD, then randomized to receive either one more cycle of the same chemotherapy, or 25.5 Gy of involved-field radiation. There was no difference in CR rates (over 90%) or EFS rate (88% at 8 years) between the two groups, although patients with large mediastinal masses (mass: thoracic ratio > 1/3) had significantly lower response rates than other patients (84% versus 90%, respectively, P < 0.001). In the Academic Medical Center in Amsterdam, in view of the observation made in Uganda, radiation has been used sparingly in the treatment of children with Hodgkin's disease since 1975 [20]. Overall, 59 children have been treated. The first 21 received MOPP, with radiation being given only to disease sites greater than 4 cm in diameter. The next 17 received ABVD alone, and the most recent series of 21 patients received alternating MOPP and ABVD, three cycles each. The majority of these patients are alive: 9 of the 59 relapsed, 6 of whom have been salvaged with subsequent MOPP or ABVD therapy, although both patients who relapsed in the most recent group, treated de novo with MOPP/ABVD, died after receiving more chemotherapy and radiation.

These data may not be sufficient to convince everybody, but in conjunction with other published series [13–18], they strongly suggest that for the majority of children with Hodgkin's disease (those with bulky mediastinal disease may be an exception), the questionable therapeutic benefit of radiation therapy is outweighed by the serious toxicities that it produces. While chemotherapy can be responsible for secondary hematological neoplasms, there is a wide range of effective drugs available to treat Hodgkin's disease today, and it would seem appropriate for current therapeutic research in childhood Hodgkin's disease to focus on chemotherapy, and to attempt to define the most effective and least toxic drug combination and the minimal duration of therapy required in various patient subgroups. Even patients with bulky disease may not require radiotherapy if improved chemotherapy regimens can be devised, while caution should be exercised in irradiating bulky tumor masses which appear to respond slowly to chemotherapy – such masses may, in many
patients, contain nonviable tumor. In this respect, attention needs to be paid particularly to young women, since mediastinal disease is common in adolescent females – the same patient group in whom radiation of breast tissue is most likely to lead to breast cancer.

**B-cell lymphomas**

Survival rates for patients with B-cell pNHL (including patients with bone marrow involvement greater than 25%, who are generally referred to as having acute B-cell leukemia) have undergone steady improvement over the last decade, and results reported at the Lugano meeting were truly excellent. B-cell pNHL consists predominantly of Burkitt’s or Burkitt-like lymphoma (REAL classification; small noncleaved-cell lymphoma in the Working Formulation), although a fraction of patients (perhaps 10%) fall into the morphological category of large B-cell lymphoma. Many of the latter have the same cytogenetic abnormalities as Burkitt’s lymphoma. Both the German Berlin–Frankfurt–Münster (BFM) cooperative group (70 centers) and the Society Française d’Oncologie Pédiatrique (SFOP) (47 centers) reported EFS rates of approximately 90% in series of 437 and 429 evaluable patients accrued since 1990 and 1989, respectively (Table 2) [21, 22]. In contrast to the situation in the diffuse B-cell lymphomas in adults, which for the most part differ biologically from B pNHL and may continue to relapse over a six-year period from presentation, the results of therapy in patients with B pNHL can be predicted within a few years of the initiation of a clinical trial, since relapse after a year is essentially unknown. Thus, these results, in conjunction with the smaller US Pediatric Oncology Group (POG) studies (Table 2), also reported at the Lugano meeting [23], and the US National Cancer Institute studies, in which similar results were achieved [24], confirm beyond any reasonable doubt that present chemotherapy regimens are capable of curing almost all children with B-cell lymphoma.

None of these protocols uses the by now standard St. Jude staging system as the sole means of stratifying patients into ‘risk’ groups which receive different therapy, probably because the St. Jude stages do not sufficiently distinguish patients with respect to the most important prognostic factor after treatment: tumor burden. In the BFM study, for example, patients were divided into three risk groups (R1, R2, and R3) which received progressively more therapy (2, 4, or 6 cycles after a cytoreductive prephase), on the basis of disease resectability, serum LDH, and bone marrow and/or CNS involvement. R1 patients had completely resected disease; R2, unresected disease with an LDH less than 500 U/l; and R3, an LDH greater than 500 or bone marrow involvement, with or without CNS involvement. EFS rates at five years were 100% for R1, 97% for R2, and 79% for R3.

Interestingly, in the previous BFM study (BFM 86), patients with St. Jude stage III disease were all treated in the R2 group, R3 being reserved for patients with bone marrow and/or CNS disease [25]. In BFM 86, the predicted EFS rate for stage III patients was 73% – no better than patients with stage IV disease (71%) or acute B-cell leukemia (78%). In the present study, in which patients with stage III disease and LDH above 500 U/l were treated with the most intensive therapy arm (R3), the outcome was clearly better – stage III patients overall having an EFS rate of 90% at five years. Although patients with stage III disease received six cycles of therapy in BFM 86, this included only 0.5 Gms MTX per m² as opposed to 5 Gms per m² in BFM 90. These data suggest that the 10 fold higher dose of MTX benefits stage III patients with higher tumor burdens, and also implies that the intensity of therapy is more important than duration – a lesson that has been repeatedly learned in this disease [24]. Patients with a serum LDH greater than 1000 U/l, however, still had a worse prognosis: EFS was 68%, compared to 95% for patients with a serum LDH less than 1000 U/l. Serum LDH, a surrogate for tumor volume, was also a better predictor of outcome than the presence of a residual mass – in other words, a residual mass was more likely to contain viable tumor in patients who presented with a higher serum LDH. This was further demonstrated by a comparison of eventual outcomes in R2 patients with residual masses versus patients with residual masses in R3. Among 32 patients in R2 with a residual mass after two therapy cycles (which included 118 patients), 1 ultimately progressed. In contrast, among 60 patients in R3 with a residual mass after two cycles (a total of 132 patients), 11 ultimately progressed.

In the SFOP study, as in that of the BFM group, patients with higher tumor burdens received longer ther-

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**Table 2. Treatment results from three cooperative groups in patients with B-cell lymphomas.**

<table>
<thead>
<tr>
<th>Cooperative group</th>
<th>Total number of patients</th>
<th>Event-free survival rates for all patients</th>
<th>Event-free survival rates in various risk groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Low</td>
<td>Intermediate</td>
</tr>
<tr>
<td>BFM (Germany)</td>
<td>437</td>
<td>91% ± 2</td>
<td>R1: 100%</td>
</tr>
<tr>
<td>SFOP (France)</td>
<td>492</td>
<td>91% ± 2</td>
<td>A: 98% ± 5</td>
</tr>
<tr>
<td>CCSG (USA)*</td>
<td>39</td>
<td>80%</td>
<td>–</td>
</tr>
<tr>
<td>Orange</td>
<td>41</td>
<td>84%</td>
<td>–</td>
</tr>
</tbody>
</table>

* Includes some patients with anaplastic large-cell lymphoma.
apy durations: patients with resected disease (group A) received two cycles of 'COPAD', while those with more than 70% bone marrow blasts and/or CNS involvement (group C) received seven months of therapy, including more intensive consolidation with high-dose ara-C, high-dose MTX (8 g/m²), and etoposide. All other patients (group B) received five cycles of therapy over a four-month period. Patients with CNS involvement also received cranial irradiation at the end of therapy. Event-free survival rates were 98% in group A, 93% in group B, and 83% in group C.

The C arm of the SFOP protocol (LMB 89) was also used by the CCSG in the United States in a randomized trial for children (<21 years) with extensive nonlymphoblastic lymphomas in which it was compared to the 'Orange' regimen, a protocol comprising sequential elements: CHOP (cyclophosphamide, Adriamycin, vincristine, and prednisone), followed by ifosfamide and etoposide, and finally by the DECAL combination (dexamethasone, etoposide, cisplatin, ara-C, and t-asparaginase), a protocol also used for patients with relapsed pNHL. Children with CNS disease received 18 Gy to the cranium and the total therapy duration was 5.5 months. EFS at 24 months for the 80 evaluable patients (41 treated with the SFOP regimen, 39 with Orange) was similar in both regimens, 80% and 84%, although toxicity did appear to be greater with the SFOP regimen (more stomatitis and longer periods required in hospital). While high-risk patients (bone marrow and/or CNS disease, LDH greater than twice normal, a mediastinal mass or thoracic nodal disease) achieved an 80% survival with the SFOP regimen and 60% on the Orange regimen, this apparent trend was not significantly different. However, there was a worse outcome for patients with large-cell lymphoma treated according to the SFOP regimen, who achieved an EFS rate of only 50% compared to 92% for patients treated with the Orange regimen (P = 0.036). At first sight, these results appear to differ from those achieved by the SFOP in 47 patients with large B-cell lymphoma in which EFS was 89% at four years. A possible explanation for the difference, however, is that the CCSG's large-cell group included T-cell lymphomas. Patients with CNS disease fared significantly worse in the CCSG study than other patients (P = 0.0098) regardless of the treatment regimen employed: EFS was 40% at two years, once again, an apparently different result to that obtained by the SFOP in which 62 patients with CNS disease, 41 of whom also had bone marrow involvement, achieved an EFS of 78% at three years.

With such remarkably good results compared to those of a decade ago, it may seem churlish to suggest that there is still room for improvement. But this does apply to the relatively small numbers of patients in the highest risk groups, although for the bulk of patients future studies will need to focus primarily on reducing therapy without sustaining a corresponding reduction in EFS rates. In some of the protocols, such reductions in therapy might prove to be relatively straightforward. In both the French and German studies, patients with the most extensive disease receive longer durations of therapy than other patients (including four maintenance cycles in the SFOP protocol). It seems probable that therapy durations for these groups could be reduced; in the NCI series, similar results to those reported in Lugano appear to be achievable in the highest risk group, even though only four therapy cycles, taking 12–15 weeks to deliver, are administered for high-risk patients [24]. While this series remains considerably smaller than the French and German studies, approximately twice the number of patients reported originally [24] have now been accrued, with no change in the results, while similar results have been achieved in Italy and Israel with this protocol, the total number of patients with B-cell lymphomas treated with this protocol now being approximately 150.

The use of cranial radiation in patients with CNS disease, as used in the SFOP protocol, can also be questioned. To date there is no evidence that it is beneficial, and it may simply add toxicity. Cranial radiation is not given in the BFM and US studies, and outcome in patients with CNS disease does not appear to be inferior.

Finally, it is legitimate to question the role of adriamycin in all of these studies. An earlier randomized CCSG study did not show an advantage to the incorporation of daunomycin, and while anthracyclines are held in high regard for the treatment of adults with high growth-fraction lymphomas, it is worth remembering that this group of lymphomas consists of a mixture of several different entities, and the results achieved are, in any event, rather poor. Elimination of anthracyclines, which, even if active, may add little therapeutic benefit to these multiagent treatment regimens, would decrease the degree of myelotoxicity and the frequency of late cardiac failure, which has been described even in patients who receive substantially lower anthracycline doses than have been associated with early left ventricular dysfunction. Of perhaps lesser importance, although worthy of consideration, is the role of corticosteroids in the treatment of B-cell lymphomas. Once again, their therapeutic contribution may be minimal in these intensive regimens (corticosteroids are not a component of the NCI protocol), and they do sometimes cause significant side effects, although their contribution to serious toxicity, such as opportunistic infections, is difficult to estimate in the setting of intensive combination therapy.

It seems obvious to ask the question whether better results might be achieved in adults with aggressive B-cell lymphomas – at least those with Burkitt's lymphoma – by the use of treatment regimens used for children with this disease. In this Lugano conference, a small series of 8 adult patients (19–65 years, median 35) with advanced Burkitt's lymphoma (7 were St. Jude stage IV and 1 stage III) were treated with an intensive chemotherapy regimen which included cyclophosphamide, Adriamycin, vincristine, high-dose ara-C and high-dose methotrexate. Six of the eight patients achieved long-term survival. This tiny series is supported by the excellent results achieved in adults treated with SFOP, BFM, and NCI protocols [24, 26, 27]. In general, the dose intensity of pediatric protocols is much higher than that of protocols designed for
adults with high growth-fraction lymphomas, particularly with respect to high-dose methotrexate and high-dose ara-C, and it is probable that this accounts for the worse survival achieved in adults with Burkitt's lymphoma treated with such regimens (50%-60%) [28]. Even patients in whom autologous bone marrow transplantation is performed in first remission appear to have a worse outcome – only a part of which is due to toxic deaths [26]. Indeed, the strategy of performing ABMT in first remission is flawed, at least if regimens only able to achieve 50%-60% CR rates are used as primary therapy. Based on published data [29], only 50%-72% of the patients who receive ABMT achieve prolonged remission, such that the cure rate will be, at best, 60 x 70, i.e., 42%. Thus, it is essential to use a regimen able to induce remission in 90% or more of all patients. Since only a few cycles of such regimens cure 90% of patients (suggesting that the first few cycles of therapy are critical), it is difficult to support an ABMT strategy with its attendant treatment delays, the theoretical risk of reinfusing tumor cells in the absence of extremely efficient purging, and the probable increased toxic death rate. These reservations are supported by the worse result achieved in patients who received ABMT in a small French series of patients treated with SFOP protocols [26].

Peripheral T-cell lymphomas

Patients with peripheral T-cell lymphomas, a term used here to include all nonlymphoblastic T-cell lymphomas, have a life expectancy that is only slightly lower than that of patients with B-cell lymphomas. Patients with anaplastic large-cell lymphoma, for example, have been treated with a protocol which incorporates some of the elements of the LMB protocols designed for B-cell lymphomas, namely, a prephase of COP with 2 COPAD-M induction courses [30]. Subsequently, however, patients received vinblastine, etoposide, bleomycin, and prednisone, alternating with a COPAD-M cycle with half the dose of cyclophosphamide (500 mg per dose for a total therapy duration of seven months. Forty-three children aged less than 17 years were entered on a study conducted in 18 centers. Data regarding CD30 (41/41 positive), epithelial membrane antigen (32/36 positive) and markers of T lineage (25/39) were available for the majority of patients. Fourteen of 19 patients tested had a 2;5 translocation. Three patients with B-cell markers were included in the series. As anticipated, only 4 patients had stage IV disease, and over half (26) had B symptoms. Almost all patients had lymphadenopathy (42), while 34 had skin lesions and 22 visceral involvement (lung in 8). Forty-one patients achieved CR, and 32 remain in first CR at a median follow-up of 30 months. Overall, 38 patients are alive one to five years after presentation, although this number includes 6 patients who relapsed and remain alive with no evidence of disease after salvage therapy (including ABMT). Thus, the overall survival rate was 86%, and EFS rate 72%, not dissimilar from recently reported BFM results [31]. Interestingly, and in contrast to some series of adult patients with this disease, children with skin involvement had a worse prognosis, as did those with lung and to a lesser extent, other visceral involvement in addition to lymphadenopathy.

Peripheral T-cell lymphomas that do not fall into the category of anaplastic large-cell lymphomas are rare in children. Among all 1044 patients younger than 18 enrolled into BFM 86 and 90 pNHL studies, for example, 161 (15%) had lymphoblastic lymphoma and 23 (2%), nonanaplastic, peripheral T-cell lymphoma [32]. Interestingly, the male:female ratio was essentially 1:1 in the latter patients, in contrast to patients with lymphoblastic lymphoma in whom males predominated 4:1. Sites of disease in these 23 patients generally included both nodal and extranodal disease – 19 had nodal involvement but only 2 lymphadenopathy alone. Extranodal disease sites included liver/spleen (11), mediastinum (8), skin (5), bone marrow (4), lung (2), bone (2), and pharynx (2). Two patients with completely resected localized disease received no treatment and remain in remission at 18 and 21 months. The majority of these patients (18) were treated with the BFM lymphoblastic lymphoma protocol, which is identical to that used for standard-risk patients with acute lymphoblastic leukemia. Only 1 was treated with the BFM B-cell protocol, and 2 received a hybrid protocol. Sixteen of the patients who received chemotherapy remain in remission for a median duration of 2.6 years (range 1–7 years). This outcome is considerably better than that achieved in adults with T-cell lymphomas, who generally have a poor prognosis; perhaps a trial of similar therapy should be undertaken in selected adult patients with T-cell lymphomas.

Newer approaches to diagnosis and treatment

Several new approaches to diagnosis and treatment were discussed at the most recent Lugano conference. PCR techniques have improved, such that longer DNA fragments can be amplified. This has enabled a higher fraction of translocations in which there is marked variability in the chromosomal breakpoint locations – in the example presented here, 8;14 translocations – to be detected [11]. Such approaches should improve the ability to correlate clinical characteristics with molecular findings, and perhaps to provide a means of detecting minimal residual disease applicable to a wider patient population. The latter is only likely to be successful in detecting translocations in peripheral blood and bone marrow, but this is the highest risk group, and the one in which such techniques are the most likely to be useful.

Of considerable value in detecting tumors bearing a 2;5 translocation are antibodies directed against the resultant nucleophosmin/ALK fusion protein, which leads to inappropriate expression of the ALK tyrosine kinase [33]. In the series reported at this meeting, a polyclonal antibody raised against the ALK portion of the fusion protein was shown to work well in formalin fixed tissue
Cancers are EBV-associated and may also be applicable to cancers, e.g., nasopharyngeal carcinoma and some breast cell death. The latter system has two layers of specificity — to cancer associated with other viruses.

Out inhibiting cell death. Such approaches have implications beyond lymphoid neoplasia — many epithelial cancers, e.g., nasopharyngeal carcinoma and some breast cancers are EBV-associated — and may also be applicable to cancer associated with other viruses.

Finally, identification of the molecular lesions present in tumor cells may have significance to treatment planning, and even to the development of novel, tumor-targeted therapy. Although it appears to be treatment protocol dependent, p53 expression in Burkitt’s lymphoma cells was reported, in this meeting, to be an important determinant of outcome, adding to the prognostic importance of tumor burden (measured as serum LDH) [9]. The incorporation of p53 expression into risk determination could permit improved stratification of patients for more and less intensive therapy. Moreover, since Burkitt’s lymphoma cell lines that bear a mutant p53 gene have been shown to be differentially sensitive to alkylating agents versus topoisomerase II inhibitors, depending upon the level of topoisomerase II in the cells [34], such information could be relevant to the design of therapy — the inclusion of both types of drug into combinations should be much more effective than either alone.

The presence of EBV in tumor cells provides a potentially exploitable target for therapy, as demonstrated in vitro by Bhatia et al. [9], who transfected cells with ‘suicide genes’ coupled to the FR region of the EBV sequence (oriP) to which the EBV EBNA-1 protein binds. This results in the expression of the suicide gene only in EBV-containing cells (which invariably express EBNA-1) — i.e., for operational purposes, EBV-containing tumor cells. Interestingly, in EBV-negative cells, the FR sequence seemed to have a suppressive effect on transcription of the suicide gene, thus further increasing specificity.

Two different suicide genes were used: either cytosine deaminase, which converts the nontoxic (to mammalian cells) 5-FC to the cytotoxic 5-FU [35], or the EBV gene, Zebra [36]. In the former case, exposure of cytosine deaminase-expressing cells to 5-FC results in cell death, while in the latter, Zebra expression induces EBV into a ‘lytic cycle’ whereby virions are produced, resulting in cell death. The latter system has two layers of specificity — only EBV-containing cells will express Zebra, and only EBV-containing cells can be killed by this protein. It was also shown that the production of large numbers of viral particles could be effectively inhibited by acyclovir without inhibiting cell death. Such approaches have implications beyond lymphoid neoplasia — many epithelial cancers, e.g., nasopharyngeal carcinoma and some breast cancers are EBV-associated — and may also be applicable to cancer associated with other viruses.

References


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