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Acknowledgements—we thank Monica Guelfi for careful data managing and Rita Lionetto for helpful support in designing the study.

Eur J Cancer, Vol. 29A, No. 5, pp. 692–698, 1993.
Printed in Great Britain

0964–1947/93 $6.00 + 0.00

Curability of Advanced Burkitt's Lymphoma in Children by Intensive Short-term Chemotherapy

Marco Gasparini, Luigia Rottoli, Maura Massimino, Maria C. Gianni, Emanuela Ballerini, Fernando Ravagnani, Sandro Pupa and Franca Fossati-Bellani

The treatment programme (regimen I) we designed in 1982 for advanced Burkitt's lymphoma was modified in 1986 as regimen IIA and IIB for patients presenting without or with bone marrow (BM) and/or nervous system involvement, respectively. Following a 5-week course of cytoreductive chemotherapy, including vincristine (VCR), cyclophosphamide (CPM), doxorubicin (DXR), high-dose methotrexate (HDMTX) and intrathecal methotrexate and cytarabine (ARAC), high-dose ARAC and cisplatin were given as a 4-day continuous infusion. Regimen I continued with an additional 3-week course including VCR, CPM, DXR and HDMTX, which was omitted in regimen IIA. In regimen IIB the initial cytoreductive chemotherapy was complemented by adding etoposide and increasing HDMTX doses, and by modifying the high-dose ARAC administration modality and was followed, once the bone marrow had recovered, by ifosfamide that concluded the programme. A total of 44 children (22 in regimen I and 22 in regimens IIA and IIB) were treated, with an overall response rate of 98%. 4 patients died as a result of treatment related complications. Survival, progression-free and event-free survival rates were 73, 70 and 63%, respectively, for regimen I, and 82, 90 and 82%, respectively, for regimen IIA and IIB. A short chemotherapeutic regimen, using alternating phase-specific and non-specific agents, is able to cure the majority of patients with advanced Burkitt's lymphoma.
Eur J Cancer, Vol. 29A, No. 5, pp. 692–698, 1993.

INTRODUCTION

BURKITT'S LYMPHOMA (Bu-L) is a highly malignant lymphoma resulting from a transformed B-cell monoclonal expansion, occurring mostly in children and in patients with congenital or acquired immunodeficiencies [1–3]. It was first recognised and described in equatorial Africa, where it still represents one of the most common malignancies in children [4]. In countries outside Africa Bu-L occurs less frequently, but represents a large proportion of childhood non-Hodgkin lymphoma [5, 6]. It has a typical clinical picture of rapidly growing masses within the abdomen involving the gastrointestinal tract, the lymph nodes, the kidney and/or the liver, often associated with malignant peritoneal effusion. Extra-abdominal lesions may occur anywhere such as skeleton, central nervous system (CNS), bone marrow (BM), subcutaneous tissue, lymph nodes and may or may not be associated with abdominal involvement [1].

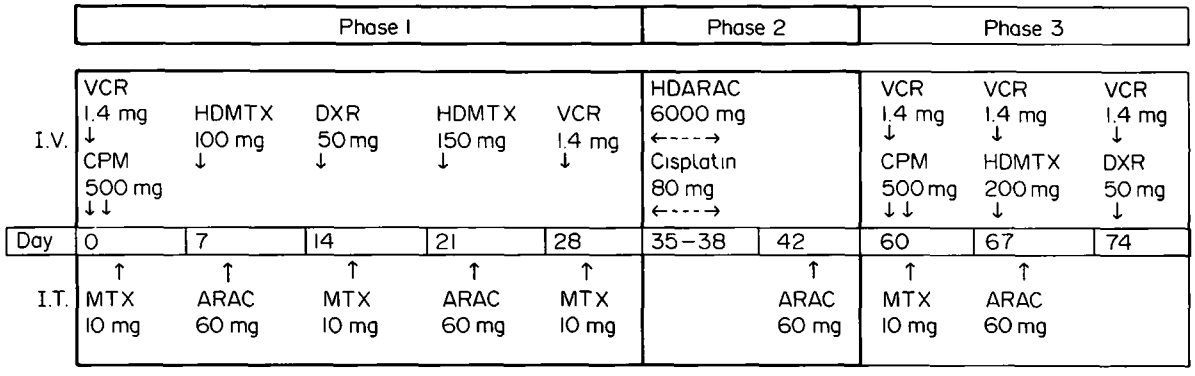

Fig. 1. Treatment scheme of regimen I (applied from 1982 to 1986 to all cases) and regimen IIA (applied from 1986 to 1990 only to patients without bone marrow and/or nervous system involvement). Regimen I consisted of phase 1 + 2 + 3. Regimen IIA consisted of phase 1 + 2. Drug doses are in mg/m² (for HDMTX in mg/kg). HDARAC and cisplatin were given as a continuous infusion, for 4 consecutive days. HDMTX was given as a 6-h infusion plus citrovorum factor rescue.

Malignant cells show an extraordinary rapid growth with a doubling time of less than 24 h [7]. This biological property is reflected in the clinical picture of fast growing neoplastic deposits often associated with metabolic abnormalities resulting from a high cell production and loss [8].

Presenting with a large burden of malignant cells, advanced Bu-L had, until recently, a poor prognosis. Despite its chemosensitivity and an initial high remission rate, early relapses frequently occurred when it was treated according to standard chemotherapeutic programmes that were successfully used for treatment of other subtypes of childhood non-Hodgkin lymphoma [9–12]. Improvement in the outcome of advanced Bu-L has been obtained in recent years by the introduction of tailored chemotherapeutic regimens designed specifically for treatment of Bu-L [13–17].

We here report the results achieved in the treatment of Bu-L in its advanced stages, by combining and sequencing different antiproliferative drugs over a short period of time.

PATIENTS AND METHODS

Treatment methods

Three treatment programmes (regimen I and subsequently regimens IIA and IIB) were employed to treat advanced Bu-L in children between 1982 and 1990.

Regimen I was active from 1982 to 1986 and its outline is described in Fig. 1. Therapy always began shortly after admission, following intravenous hyperhydration, urine alkalinisation and administration of allopurinol and/or uricase in order to induce an adequate urine output and to prevent or minimise acute tumour lysis syndrome. Cyclophosphamide (CPM), vincristine (VCR) and doxorubicin (DXR) were given intravenously at the times shown in Fig. 1. High-dose methotrexate (HDMTX) was administered as a 6-h infusion with a 12-h intravenous prehydration and 48-h posthydration followed by citrovorum factor rescue (standard dose 15 mg) starting 24 h from the beginning of HDMTX infusion and continuing every 6 h for 12 doses. If the creatinine clearance was lower than 60 ml/min at the time scheduled for the first HDMTX, this drug was postponed for 1 week and replaced by DXR. High-dose cytarabine (HDARAC) and cisplatin were administered as a continuous 4-day intravenous infusion at a total dose of 6000 mg/m² and 80 mg/m², respectively. Intrathecal chemotherapy was given regardless of signs of overt CNS involvement. Total planned duration of the programme was 78 days.

This regimen was modified in 1986 to define two different programmes for patients without (regimen IIA) or with (regimen IIB) involvement of BM and/or CNS.

Regimen IIA, applied to children without overt BM and/or CNS infiltration, was identical to regimen I, with the exception that intravenous chemotherapy planned after HDARAC and cisplatin was deleted (as seen in Fig. 1). Total planned duration of regimen IIA was 53 days.

Regimen IIB was introduced for patients who presented with CNS involvement and/or BM infiltrated by blasts in excess of 25% (Fig. 2). It followed the strategy applied for regimens I and IIA with the following changes. Treatment phase 1 preceding the HDARAC + cisplatin infusion was altered by escalating the HDMTX doses and introducing etoposide as an additional drug, given 7 days after the first HDMTX in two daily doses of 250 mg/m² 12 h apart. The administration modality of HDARAC in the phase 2 of the regimen was modified to give a continuous 4-day infusion of 4000 mg/m² with an additional intravenous push dose of 750 mg/m² daily for 4 days. Following bone marrow recovery from HDARAC + cisplatin, the programme was concluded by a 24-h infusion of ifosfamide (IFO) at the dose of 8000 mg/m², along with an equal amount of intravenous mesnum to prevent cystitis (phase 3). The planned duration of this programme was 65 days. No additional therapeutic measures were planned nor utilised for either regimen. Surgical exploration could be considered in patients with residual mass(es) prior to the HDARAC + cisplatin administration. Upon completion of therapy, all children were regularly followed-up and monitored for relapse or treatment-related side effects at progressively increasing intervals of time. All children are still on active follow-up.

Complete remission was defined as the complete regression of all signs and symptoms of disease evaluated clinically and pathologically. Regression of more than 50% in volume of neoplastic masses with complete clearing of blasts in BM and

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Revised 28 July; accepted 31 July 1992.

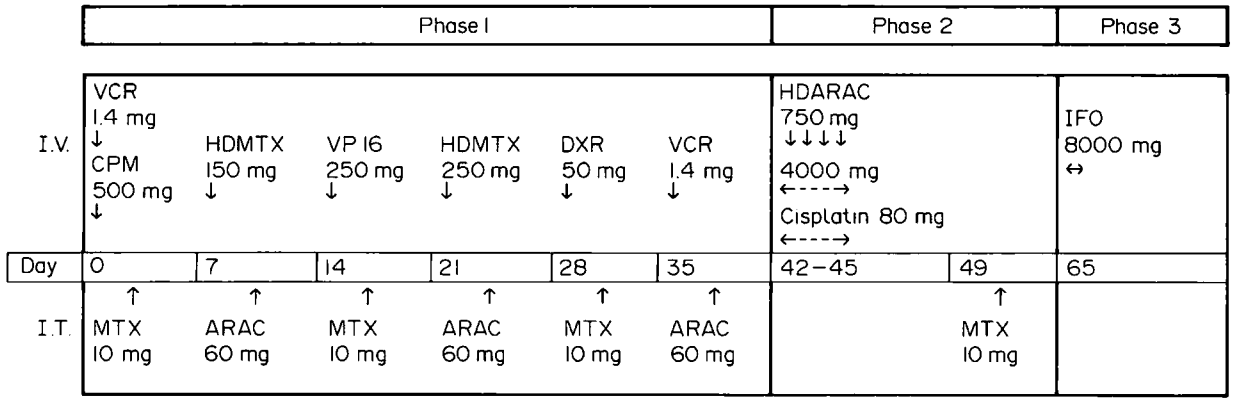

Fig. 2. Treatment scheme of regimen IIB (applied from 1986 to 1990 only to patients with bone marrow and/or nervous system involvement). Drug doses are in mg/m² (for HDMTX in mg/kg). HDARAC was given as a continuous infusion (4000 mg) plus one daily push (750 mg), for 4 consecutive days. HDMTX was given as a 6-h infusion plus citrovorum factor rescue. IFO was given as a 24-h infusion plus mesnum.

CNS, if present at the time of diagnosis, was considered as partial remission. The remission status was evaluated before and after the completion of phase 2 of each regimen, as well as at the end of the entire treatment programme.

Survival (SURV) was calculated in months from the time of treatment commencement to the time of death or last follow up visit. Progression-free (PFS) and event-free survival (EFS) were calculated as months elapsing from treatment start to the time of relapse and to the time of relapse or death from any cause, respectively. Survival rates were calculated according to Kaplan and Meier [18].

Patients

A total of 44 consecutive newly diagnosed Bu-L patients were treated. There were 38 males and 6 females, with a median age of 9 years and 6 months (ranging 2 years and 6 months to 15 years and 8 months).

22 were entered in regimen I between 1982 and 1986. From 1986 onwards, two additional groups (consisting of 14 and 8 patients, respectively) were managed according to regimens IIA and IIB.

Tissue material for histological diagnosis of Bu-L was available in 39 cases. In the remaining 5 children the diagnosis was based on cytological examination of malignant cells drained from peritoneal effusion. The morphological diagnosis of Bu-L was based essentially on the criteria described by Lennert and co-workers [19, 20].

In 32 of the 44 cases, cell suspensions from fresh tumour specimens were available for immunophenotypic analysis by means of fluorescence activated cell sorting, which confirmed the histological diagnosis in each case. Details of this analysis have previously been reported [21].

Staging procedures were usually completed within 24 to 48 hours of admission and in addition to routine biochemistry, chest X-ray, abdominal sonography and skeletal survey, bone marrow aspiration and bone marrow needle biopsy from iliac crests as well as spinal fluid cytology and chemistry were performed. Computerised axial tomography and/or nuclear magnetic imaging were employed to evaluate specific sites of disease, especially within the abdomen or the CNS. In selected cases, bone scan, gallium scan, upper gastrointestinal X-ray examination, or barium enema were performed. Clinical details at presentation are summarised in Table 1. Abdominal involvement was present in 34 of the 44 patients and consisted of huge multiple masses associated with ascytis in 12, involvement of the gastrointestinal tract with diffuse mesenteric and/or retroperitoneal adenopathies in 16, multiple liver deposits in 3 and ovarian and uterus involvement in 3. In the 16 patients with recognisable gastrointestinal tumours, large bowel, ileum, stomach and jejunum were involved in 9, 5, 1 and 1 patients, respectively. In addition to the 3 patients with liver involvement at diagnosis, 8 additional children with abdominal tumour had unequivocal signs of liver infiltration.

Of the 34 patients with abdominal lymphoma 17 showed synchronous extra-abdominal disease in one or multiple sites.

Of the 10 cases presenting with BM involvement, 5 showed almost total marrow replacement by blasts, which were recognisable in the peripheral blood in only 1 patient.

As shown in Table 2, patients were staged according to the systems proposed by Ziegler [1] and by Murphy [9].

At treatment initiation, according to WHO criteria [22], only 7 patients had a performance status of 1, while 13 and 24 were graded as 2 or 3, respectively. 11 cases had a nutritional quotient lower than 80%. 5 patients had impairment of the renal function with a creatinine clearance of less than 40 ml per minute, and 16 presented with hyperuricaemia. In 9 cases lactate dehydrogenase

Table 1. Sites of involvement at diagnosis

Sites of involvement	No. of patients
Only abdominal	17
Abdominal and extra-abdominal	17
Pleura (+ CNS) (+ Testis)	4 (+1) (+1)
BM	3
Maxilla (+CNS)	3 (+2)
Skeleton + BM +CNS	1
Rhinopharynx	1
Mediastinum	1
Only extra-abdominal	10
Maxilla + BM + CNS	4
Maxilla + CNS	2
Rhinopharynx + Bilat. Nodes	2
Rhinopharynx + BM	1
Skeleton + BM	1
Total with BM involvement only	5
Total with CNS involvement only	5
Total with BM + CNS involvement	5

CNS = central nervous system; BM = bone marrow.

Table 2. Relapses related to stage and treatment regimen applied in 40 evaluable patients

Treatment regimen	Relapsed/ total	Staging system: Ziegler's [1] B	C	D	Murphy's [9] II	III	IV
Regimen I	*6/20	1/5	2/9	3/6	—	3/13	3/7
Regimen IIA–IIB	2/20	1/5	1/5	0/10	0/2	1/10	1/8
Total	*8/40	2/10	3/14	3/16	0/2	4/23	4/15

*Including 1 non-responder and 2 late "relapses".

(LDH) levels were between 500 and 1000 IU/ml and in a further 20 levels were greater than 1000 IU/ml. While a slight elevation of transaminases was documented in 17 patients, hyperbilirubinaemia was observed in only 6 with a prevalence of the conjugate fraction.

RESULTS

Treatment results

Before starting HDARAC + cisplatin (phase 2 of each treatment regimen), a complete and partial remission status was achieved in 37 and 6 patients, respectively, for an overall response rate of 98%. Only 1 patient progressed after transient signs of response to chemotherapy. The remission status was assessed clinically in the majority of cases. In 5 cases, because of persistent residual mass(es) prior to HDARAC + cisplatin, a surgical exploration was performed and in 4 no evidence of lymphoma was documented. 4 additional children required laparotomy because of complications such as bowel perforation (3 cases) or occlusion (1 case) before this treatment phase, and the clinical complete remission status was pathologically confirmed in each instance.

Following the HDARAC + cisplatin administration, all the 6 partial reponders underwent a complete remission.

Of the 43 patients with a complete remission, a total of 7 relapsed, 3 while on treatment soon after the phase 2 of the regimens, and the remaining 4 at 1 (2 cases), 12 and 26 months after completion of the treatment programme. The 5 children who relapsed while on treatment or shortly afterwards subsequently died of their disease. The two patients with later relapses were salvaged by a second course of the same treatment regimen used for their initial therapy.

4 children died in complete remission, because of treatment-related complications during regimens I (2 cases) and IIA (2 cases).

Relapses according to stage and treatment regimen in the 40 evaluable patients are shown in Table 2.

Of the 20 evaluable patients treated with regimen I, 6 showed disease progression, including the unresponsive patient and the 2 late relapsers. Of the 4 patients with an early failure, 3 had BM and/or CNS infiltration at presentation. The fact that 3 of 7 patients with this pattern of clinical presentation had an early failure in regimen I, prompted us to introduce treatment modifications resulting in regimens IIA and IIB, that differentiated the treatment programme for patients with or without BM and/or CNS involvement at diagnosis.

Only 2 of the 20 evaluable children treated according to these last regimens failed, while on therapy and one month from its discontinuation, respectively, and both died of progressive disease. Therefore only 1 of the 8 with BM and/or CNS involvement at diagnosis relapsed. No late recurrences have been observed so far after a median follow up of 30 months (range 20–56 months).

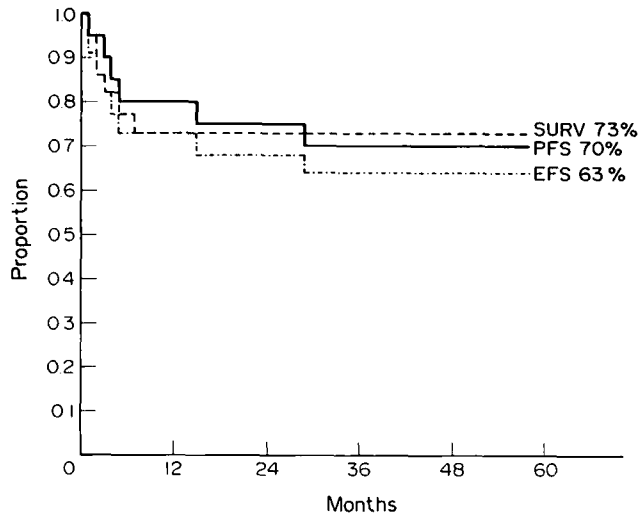

Fig. 3. Survival (SURV), progression-free (PFS) and event-free (EFS) survival of the whole series of 44 children.

Survival, progression and event free survival of the whole series and of patients treated according to regimens I, IIA and IIB are shown in Figs 3, 4 and 5, respectively.

Toxicity

Toxicity from these regimens was often severe and life threatening, as expected, and was responsible for the death of 4 patients (9%).

Some impairment of the renal function resulting from massive tumour destruction at treatment start was observed in one third of cases and was generally reversible within a few days. Because of an incomplete recovery of the renal function by the time of the first scheduled administration of HDMTX, this had to be postponed and replaced by DXR in 4 cases.

In 2 children a few sessions of haemodialysis were necessary to regain a normal renal function.

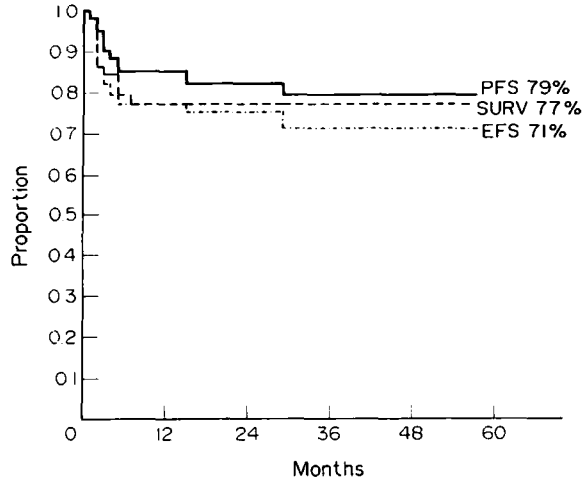

Fig. 4. Survival (SURV), progression-free (PFS) and event-free (EFS) survival of the 22 children treated according to regimen I.

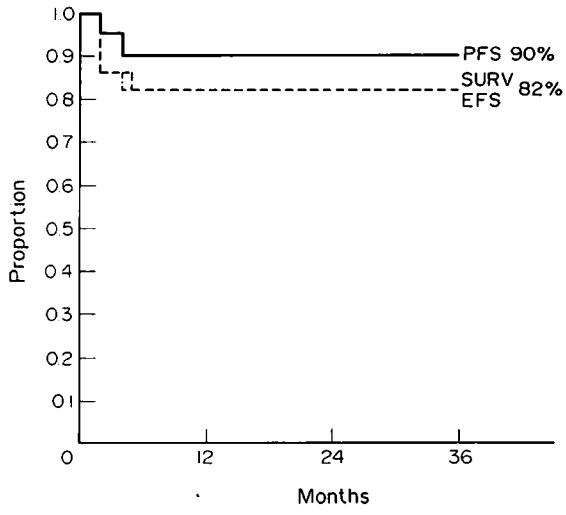

Fig. 5. Survival (SURV), progression-free (PFS) and event-free (EFS) survival of the 22 children treated according to regimen IIA (14 patients) and regimen IIB (8 patients).

Myelosuppression and infections represented the most important side effects of the entire treatment programmes especially during phase 2 of each regimen.

During phase 1 of all the three regimens, severe leukopenia [white blood cells (WBC) $< 1 \times 10^9$/l] and thrombocytopenia (platelets $< 75 \times 10^9$/l) were observed in 55% and 34% of the patients, respectively. These effects were generally reversible in a few days and platelets transfusions were necessary in 3 cases. Infectious episodes requiring antibiotics occurred in 80% of patients.

During phase 2, myelosuppression was invariably severe and prolonged. WBC dropped well below 0.5×10^9/l in 95% of patients at a median time of 3 days (range 1–7) from the end of infusion and remained $< 1 \times 10^9$/l for a median of 9 days (range 3–17). Platelets counts lower than 25×10^9/l were observed in 83% after a median time of 5 days (range 1–8) from HDARAC + cisplatin discontinuation and persisted less than 75×10^9/l for a median time of 10 days (range 4–23). Packed red cells and platelets transfusions were given to 95% and 62% of children, respectively. In 95% of patients antibiotics were required to treat fever, albeit positive blood culture for bacteria and fungi were obtained in 30% and 5%, respectively.

Nausea and vomiting were constant during the HDARAC + cisplatin administration, and anorexia persisted long after its discontinuation in the majority of children. Total parenteral nutrition was maintained for periods ranging from 7 to 21 days in about half of the patients.

No case of neurological toxicity was observed. Other side effects attributable to HDARAC were mild and transient and consisted of diarrhoea, conjunctivitis, skin rash and ptyalism.

A few days following the HDARAC + cisplatin infusion a frank diastolic hypertension was recognised in 20% of children along with transient signs of mild impairment of renal function. In each case, hypertension was successfully managed with calcium antagonists and/or beta-blocking agents and was reversible within 7–60 days.

Of the 4 treatment related deaths, 3 occurred because of septic shock during phase 2 at 1, 3 and 12 days, respectively, from the end of HDARAC + cisplatin administration. The fourth patient died owing to lactic acidosis resulting from pre-existing malnutrition and infection during phase 1 of regimen I.

Toxicity from phase 3 of regimen I consisted mainly of marked but reversible episodes of myelosuppression. An abnormal clearance of HDMTX was not observed. As for phase 3 of regimen IIB, acute reversible encephalopathy from IFO occurred in 1 of 8 children, and it was associated with transient impairment of renal function and signs of tubular damage.

The severity of side effects occurring during the treatment phases produced some delays in the timetable of the scheduled therapy. The duration of regimen I, planned as 78 days, resulted of 80 to 129 days (median 110). Regimen IIA, planned for 53 days, was completed in a median of 63 days (range 54–75). Regimen IIB required a median of 78 days (range 68–102) to be completed, while it was planned to last 65 days.

While acute toxicity from these regimens was severe, late sequelae were negligible.

DISCUSSION

These results confirm the validity of a treatment strategy consisting of intensive chemotherapy of a relatively short duration. The treatment program was designed such that antiproliferative drugs could be given as frequently as possible in a non-repetitive way, assuming that cells surviving after each drug exposure might be resistant to the previously administered compound. Because of the necessity of starting therapy as soon as the diagnosis of non-Hodgkin lymphoma was established, we decided to initiate with the administration of CPM, well known to be active in Bu-L [23] in association with VCR, since this represented the first treatment step of all ongoing treatment programmes for the other subtypes of childhood non-Hodgkin lymphoma.

Because of the high proliferative rate of Bu-L and the necessity to minimise intervals between therapy (when there may be tumour regrowth), we also introduced MTX at high doses. HDMTX can reach cytocidal levels in the CNS and in appropriate dosages can overcome some forms of cell resistance [24]. Bu-L was previously treated in a similar way to other sybtypes of childhood non-Hodgkin lymphoma. Even though a high initial complete remission rate could be easily obtained, early relapses, resulting from the rapid development of resistant cell clones, were frequent [9–12]. In designing this programme we assumed that by the end of phase I of the treatment regimen the majority of patients would be in complete remission. In this condition, residual cells surviving after previous drug exposure, might be in the best condition to proliferate. For this reason we selected to administer at that time another antimetabolite (ARAC), which could optimally exert its activity on cells in the S phase [25]. ARAC was given as a 96 h infusion in order to continuously expose the dividing cells over a protracted period of time since their presumptive doubling time is approximately 24 h. Cisplatin was combined to HDARAC because of the synergistic activity shown in experimental setting [26] and the results previously obtained in a pilot study where this combination produced six complete responses in 6 cases of progressive Bu-L resistant to conventional chemotherapy. HDARAC can attain therapeutic levels in the CNS. With the high potential CNS recurrence rate in this tumour, such high concentration of systemically administered drugs is important, since intrathecally administered compounds do not reach uniform distribution throughout the cerebrospinal fluid pathways [27].

We believe that the crucial feature contributing to the eradication of all malignant cells was the combination of HDARAC + cisplatin at the time when lymphoma burden was at a minimum following the initial cytoreductive treatment of the phase 1. In

fact, prolonging therapy after HDARAC + cisplatin was not necessary, at least for patients presenting without BM and/or CNS involvement, as demonstrated by the results obtained by the more recent programme (regimen IIA) where systemic therapy was concluded at this point. For patients presenting with involvement of the BM and/or CNS, which are recognised as poor prognostic indicators [14, 15, 28], the original treatment programme was intensified, resulting in regimen IIB. Assuming that in these patients a larger tumour burden might be initially present, a more intensive cytoreducive chemotherapy was used and doses of HDMTX and HDARAC were increased in order to produce higher drug concentrations within the CNS. An alkylating agent such as ifosfamide, given in a single large dose, was further administered with the aim of killing resistant or resting residual cells after the HDARAC + cisplatin infusion. Results obtained by regimen IIB showed an improvement over regimen I, though one must comment that the number of patients treated is small.

Regimens IIA and IIB achieved a 90% progression-free survival, but the event-free survival was only 82% because of treatment-related fatalities.

These results compared favourably with those of recent trials. Sullivan and Ramirez [13] cured 10 of 14 stage III and IV Bu-L cases with a 4-drug regimen including HDMTX of 30–54 weeks duration. Murphy and co-workers [15] reported an 81% 2-year PFS in 17 stage III patients using a 6-month treatment programme, that was however far less successful for patients presenting with signs of BM and/or CNS infiltration or frank B-cell (SIg+) acute leukaemia. The French Paediatric Oncology Society reported in 1986 the results achieved in a series of 114 cases with stage III and IV high grade B-cell lymphoma, treated with a 1-year intensive nine drug regimen including HDMTX [14]. Despite a high toxic death rate, the event-free survival for patients without CNS involvement was 73%, and only 19% for those with initial CNS infiltration. The same group organised a subsequent randomised study to evaluate the possibility of reducing treatment duration to 4 months, excluding the cases with overt CNS disease at diagnosis. Results in a series of 216 children were recently reported to be similar to those of the previous study, with a toxic death rate lowered to 6%, thus confirming that there is no need for a long treatment duration in patient without CNS involvement [16]. Schwenn *et al.* [17] used a 2-month programme similar for timing and drug selection to our regimens, including both HDMTX and HDARAC. They treated 20 advanced Bu-L cases and obtained an event-free survival of 92% and 50% in stage III and IV patients, respectively, reporting 1 fatality.

Our last treatment programmes were generally concluded in 2–2.5 months, and the high PFS rate demonstrates that a longer therapy is not necessary. In the series of patients treated according to regimen I, 2 patients had 'late' relapses, however, both were cured by re-applying the same treatment programme. It is possible that instead of relapse both had a second Bu-L, event that was reported to occur in a few cases [29, 30]. Unfortunately, we were not able to investigate this possibility in our patients since we had no frozen specimens from initial biopsies to carry out molecular biological studies.

Our results as well as those reported by others confirm that advanced Bu-L is curable in the majority of children with a relatively short and intensive chemotherapeutic programme, even in the presence of CNS and/or BM involvement. Regimen IIB that was used in these cases was able permanently to eradicate the disease in 7 of 8 patients, encouraging us to continue in this direction to confirm these results in a larger number of patients.

A limit resulting from the intensive treatment applied in advanced Bu-L was represented, in our and others' experience, by the incidence of toxic deaths, and since it is unlikely that comparable results may be obtained by reducing the intensity of treatment, current efforts are focused on improving supportive therapy in order to minimise treatment related fatalities.

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Eur J Cancer, Vol. 29A, No. 5, pp. 698–703, 1993.
Printed in Great Britain

0964–1947/93 $6.00 + 0.00

Adjuvant Combination Chemotherapy (AMF) Following Radical Resection of Carcinoma of the Pancreas and Papilla of Vater—Results of a Controlled, Prospective, Randomised Multicentre Study

Kâre E. Bakkevold, Bo Arnesjø, Olav Dahl and Brit Kambestad

Between 1984 and 1987, 61 radically resected patients with carcinoma of the pancreas (n=47) or the papilla of Vater (n=14) were randomised either into postoperative adjuvant combination chemotherapy (AMF); 5-fluorouracil 500 mg/m², doxorubicin 40 mg/m², mitomycin C 6 mg/m² (n=30) once every 3 weeks for six cycles, or into a control group (no adjuvant chemotherapy) (n=31). The median survival in the treatment group was 23 months compared with 11 months (P=0.02, median test) in the control group, dependant on a survival benefit in the treatment group during the initial 2 years (P=0.04 generalised Wilcoxon). The long-term prognosis was the same with an identical survival after 2 years (P=0.10, power = 0.83). The observed 1, 2, 3 and 5-year survivals in the treatment group were 70, 43, 27 and 4% compared with 45, 32, 30 and 8 in the control group. 1 patient succumbed to sepsis probably attributable to chemotherapy. Cardiotoxicity and nephrotoxicity were recorded in 2 patients. These results suggest that adjuvant chemotherapy does postpone the incidence of recurrence in the first 2 years following radical surgery but increased cure rate was not observed.
Eur J Cancer, Vol. 29A, No. 5, pp. 698–703, 1993.

INTRODUCTION

THE INCREASING incidence of pancreatic carcinoma and the dismal prognosis represents a therapeutic challenge [1]. At present, radical surgery is the only modality with curative potential. The prognosis, however, is poor even in radically resected patients who have a 5-year survival of 0–18% [2–10]. Extended radical resections, therefore, have been introduced in order to improve long-term survival [11]. Such procedures are followed by a high complication rate [3, 5, 10, 12, 13]. In addition, they do not improve long-term survival [4, 6–10], with the exception of one study where a 5-year survival of 33% was reported [14]. The prognosis after resection of "early" pancreatic carcinoma seems to be a little more favourable and 5-year survival rates of 30% have been reported [15]. The prognosis after radical resection in carcinoma of the papilla of Vater is substantially better with reported 5-year survival rates within the range of 27–45% [2, 4, 10].

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Revised 17 June 1992; accepted 22 June 1992.