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The Epipodophyllotoxin VP16-213 in Combination Chemotherapy for Adults with Acute Nonlymphoblastic Leukaemia

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A. Introduction

Combination chemotherapy programmes that include cytosine arabinoside and an anthracycline antibiotic can cure adult patients with acute nonlymphoblastic leukaemia [1]. Furthermore, clinical trials using these two agents in different schedules [2] and in combination with other active drugs [3] has impressively improved complete remission rates [4]. It is an unfortunate fact that random leukaemic relapse characterises survival curves for most reported treatment programmes so that a major discrepancy persists between improving figures for complete remission and those for survival beyond 5 years [5]. Further improvement in cure rate confronts the clinical scientist with two major challenges. First, remission rates must be improved, and here stratification of patients on the basis of prognostic factors [6] to the most appropriate chemotherapy to balance efficacy against toxicity requires clarification. Second, the durability of complete remission must be improved and therapeutic approaches have included varying maintenance schedules, drug intensification, immunotherapy and the increasing use of bone marrow transplantation [7]. Unfortunately, although results from clinical trials are published [8], there is a striking paucity of well-controlled randomised studies in the scientific literature to provide authoritative statements on these controversial issues [9]. We report the experience with 232 consecutive patients treated at a single institution in four consecutive trials, the last of which is still in progress, examining some of these variables.

B. Materials and Methods

Individuals over the age of 14 years with a confirmed diagnosis of acute leukaemia were eligible for studies approved by the University Ethics Committee, and participated after having given informed consent. Routine haematologic assessment included morphological and cytochemical characterisation of the leukaemic subtype, and following its introduction all patients were classified according to the French–American–British (FAB) recommendations [10]. Plasminogen activator was measured as previously described [11, 12]. Venous access was ensured using a standardised method [13]. All patients received full supportive care, including protocol management with appropriate antibiotics for infectious episodes, granulocyte [14] and platelet [15] support from our own standardised programme.

The four successive studies employed different chemotherapy regimens. In study 1 [16] (80 patients) daunorubicin (55 mg/m^2) was given on day 1 and cytosine arabinoside (70 mg/m^2) by continuous infusion on days 1–5. In study 2 [17] (40 patients) VP16-213 (60 mg/m^2) was given on days 1–5, cytosine arabinoside (75 mg/m^2) by

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Table 1. Summary of 232 patients in four consecutive studies at the University of Cape Town. Study 3A is a short intensification (6 months) and 3B is an extended intensification (15 months). In study 4, C represents patients being treated with the Cape Town Regimen (CTRIII) and D those being treated with DAT

Measurement	Study 1	Study 2	Study 3		Study 4	
			A	B	C	D
Patient numbers	80	40	26	26	30	30
Complete remission (%)	30	48.5	44	44	46	46
Duration of complete remission (weeks)	28	48	44	44	>24	>24
Courses						
Number	4	1	1	1	1	2
Range	3–8	1–3	1–3	1–3	1–3	2–4
Survival of responders (weeks)	58	60	95	75	>42	>42
Long survival (%)						
10 years	2					
5 years	2	2.5	8			
2 years	15	2.5	30			

A = short intensification (6 months); B = extended intensification (15 months); C = CTR III; D = DAT

continuous intravenous infusion on days 1–5 and doxorubicin (40 mg/m²) on day 6. In study 3 [18] (52 patients) the identical induction regimen was used and patients in complete remission randomised to short intensification (6 months) or extended intensification (15 months) using 3 months of escalating cyclophosphamide followed by 3 months of vincristine, methotrexate and escalating cytosine arabinoside. In the present study, which is continuing (60 patients to date) the same three-drug induction programme (Cape Town Regimen/CTR III) was directly compared with a combination of doxorubicin (50 mg/m²) on day 1, cytosine arabinoside (200 mg/m²) on days 1–5, and thioguanine (200 mg/m²) on days 1–5 (DAT); the patients in complete remission were randomised to the same short or extended intensification regimens as study 3.

C. Results of the Four Studies are Shown in Table 1.

D. Comments

The complete remission rate in study 1 compared with those described with the same regimen from St. Bartholomew's Hospital [19] is attributed to the late referral of patients resulting in early deaths of type V failure [17, 20]. This pattern has persisted in the ensuing studies, emphasising the inappropriateness of comparing results of studies from different institutions where major variable factors such as nutritional status and clinical condition of patients on admission may differ so widely that valid comparison is impossible. Similarly, this observation emphasises the importance of meticulous demographic description of the patient population being treated and the value of the randomised clinical trial which will control for such factors and without consideration of which the efficacy claimed for different regimens reported from centres having their own characteristic patient populations is very likely to be invalid.

The epipodophyllotoxin VP16-213 included in study 2, where the patient populations are comparable, shows a clear increase in complete remission rate and an anticipated improvement in duration of remission and survival of responders. These benefits are statistically significant and occur with a shorter period of induction since the median number of courses to complete remission is reduced from four to one, and this difference is also significant. These two

studies support the conclusion that addition of the epipodophyllotoxin VP16-213, which is known to have activity in adult acute nonlymphoblastic leukaemia as a single agent, represents an advance over the use of cytosine arabinoside–anthracycline antibiotic combination.

The duration of intensification chemotherapy was assessed in study 3, and while there is a trend in favour of a short period of intensification, this difference is not statistically superior to extended treatment. In view of the small numbers involved a β, or type II, effect may obscure significant benefit, and further studies are in progress to accumulate the necessary number of patients to overcome this theoretical objection. These findings are consistent with other available controlled evidence that prolongation of maintenance or intensification therapy is, at best, of limited value once complete remission has been consolidated.

Comparison of DAT and CTR III in a currently active prospective randomised study shows no benefit for replacement of the epipodophyllotoxin VP16-213 by thioguanine in regimens already containing cytosine arabinoside and an anthracycline antibiotic. Furthermore, the greater quantities of cytosine arabinoside used in the DAT programme appear to be without additional benefit and a theoretical explanation may be synergism between epipodophyllotoxin and cytosine arabinoside [21]. In this regard, it remains to be established whether, in the particular population being treated at this institution, further drug escalation, as in a 7-and-3 regimen [22] or the Barts 10 programme, would improve remission rates by decreasing the number of patients with primary drug resistance (type I or type II induction failure) without a commensurate loss due to excessive toxicity (type III or type IV induction failure). Similarly, it is now also necessary to prospectively compare increasing amounts of cytosine and anthracycline in patients randomly receiving the same amount of these two agents in combination with the epipodophyllotoxin; such a study is currently being developed.

Prognostic factors provide the most useful basis for stratification [23]. However, our own studies have failed to show statistical correlation between remission rate or survival with the FAB classification, age, in vitro bone marrow culture [24], initial white cell [25], platelet or blast count [26]. Our experience shows the best correlation to be with patients's achievement of complete remission, and that this appears to correlate closely with the species of plasminogen activator secreted in vitro by leukaemic blasts [11, 12]. Data from study 3 and study 4 have been reanalysed following stratification using this criterion, and to date all individuals secreting the 70 000 daltons or tissue species of plasminogen activator have shown primary drug resistance to regimens containing conventional doses of cytosine arabinoside and an anthracycline antibiotic, whether in combination with thioguanine or the epipodophyllotoxin VP16-213. In contrast, those secreting either the urokinase or a mixed pattern have a complete remission rate in excess of 80% with the same induction chemotherapy. Clearly, biological stratification of previously untreated adults with acute nonlymphoblastic leukaemia on the basis of their plasminogen activator status, at least in our experience, appears to provide a rational means for selecting chemotherapeutic programmes. Support for this concept is found in preliminary experience (P. Jacobs, unpublished work) that high dose cytosine arabinoside [27] is effective salvage therapy in such individuals.

E. Summary

A total of 232 previously untreated adults with acute nonlymphoblastic leukaemia were consecutively entered into four successive studies. In the first, complete remission rates and survival were inferior to a group treated on the same regimen in London, suggesting population differences, possibly on the basis of late referral and poor nutritional status. In the second study the addition of the epipodophyllotoxin VP16-213 to conventional doses of doxorubicin and cytosine arabinoside improved complete remission rate and median duration of survival. In the third study this induction programme was unchanged and short duration of intensification was com-

pared with an extended period, but no statistically significant difference was demonstrated. In the fourth study, which is currently active, the role of the epipodophyllotoxin VP16-213 (Cape Town Regimen/CTR III) was compared with the same two agents in combination with thioguanine (DAT), but to date no difference in remission rate or survival is evident. Four conclusions are supported by data from these studies. First, the addition of VP16-213 to doxorubicin and cytosine arabinoside improves complete remission rate, prolongs median duration of complete remission and survival, with shortening of the time taken to achieve this status in our population. Second, evidence to date shows no advantage for the DAT programme containing thioguanine over CTR III in which this latter agent is replaced by the epipodophyllotoxin VP16-213. Third, there is no statistically significant difference in survival once patients have achieved complete remission following randomisation to receive 6 months in comparison with 15 months of intensification therapy. Finally, of the previously described prognostic factors, only response to initial chemotherapy has proved significant. However, our recent experience indicates that the species of plasminogen activator secreted by the leukaemic blasts allows identification of patients with primary drug resistance to regimens containing conventional doses of cytosine arabinoside and doxorubicin, and may offer a practical approach to initial use of alternative chemotherapy, particularly high dose cytosine arabinoside.

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