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Prognosis and Treatment of Acute Lymphoblastic Leukemia

Study of 650 Patients

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Summary. *The complete hematological remission (CHR) rate, duration of remission and survival were studied in relation to age, peripheral blast cell (PBC) count, presence or absence of tumor masses, cytological type, and treatment in 650 patients with acute lymphoblastic leukemia. Prognostic factors were considered separately and divided into prognostic classes. Age and PCB count correlated with both the rate and the duration of CHR. This correlation was still observed for more recent treatment schedules though it appears to be becoming progressively less significant. Meningeal relapses were more common in patients less than 1 year old and in those with a high PCB count. It is suggested that stratification of patients according to such factors as age, PCB count, presence or absence of tumor, and cytological type might be necessary for the design of new treatment protocols and for the evaluation of their results.*

Introduction

From 1955–1970, the discovery of new drugs and the application of new therapeutic modalities enabled rapid progress to be made in the treatment of acute leukemias. It was through the study of large numbers of patients in randomized trials that new forms of therapy were tested against standard ones, thus allowing objective appraisal in comparable, albeit heterogeneous, populations.

It appears that the time has come for a more critical analysis of these results. Current therapeutic achievements as well as failures suggest the importance of prognostic factors which were disregarded or unknown when the disease was uniformly fatal. These factors would lose their importance if regularly curative therapy were available. We are of the opinion that several prognostic factors should be taken into account when deciding on the indications for treatment and the mode of therapy in the individual patient with ALL. These factors will also provide a more solid basis for objective comparison of the efficacy of different treatment modalities.

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Materials and Methods

Six hundred fifty ALL patients of the hematology department, Hôpital Saint-Louis, Paris, were included in this study. Cytologic diagnosis was obtained by May-Grünwald-Giemsa stains and systematic stains for PAS, peroxidase, acetate esterase and its inhibition by sodium fluoride (Professor G. Flandrin). Different treatment protocols were used and details of these are shown in Table 1. Statistical significance between remission and survival curves was calculated by Greenwood's method, which allows accurate comparison of actuarial curves by expression of their variance.

The distribution of several pretreatment prognostic factors according to treatment protocols for the 650 patients is shown in Figure 2. Although the PCB count is a continuous prognostic variable, patients with 100,000 PCB/mm^3 having a poorer prognosis than those with 40,000 PCB/mm^3 (Bernard et al., 1973), our analysis showed that the most discriminating cut-off point was 35,000.

Age has long been known to be a prognostic factor (Jacquillat et al., 1973b). In this study the age groups considered were: less than 1, 1–15, 15–20, and over 20 years. The majority of patients (476/650) fell into the 1–15 age group, and although differences may exist within this group it was not subdivided further.

The 'tumor group' was defined by the presence of lymph nodes exceeding 3 cm in diameter, regardless of site, or an enlarged liver or spleen palpable 3 cm below the costal margin. Mediastinal node involvement was uncommon and has already been shown to be associated with a poor prognosis (Ravindranath et al., 1975).

Another important prognostic factor is cytologic type, which unfortunately was known in only 216 of the 650 patients.

Immunological assay for surface membrane markers was performed in 100 patients.

Finally, the 650 patients were divided into three classes on the basis of the number of poor prognostic factors represented by age,

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Table 1. Comparison of the treatment protocols used in this study

	< 20 years old						
	02-04 LA 64	ALGB 6601	06 LA 66	ALGB 6801	01 LA 69	ALGB 7111	01 LA 72
Induction	Pred + VCR	Pred + VCR	Pred + VCR + DNR (once weekly)	Pred + VCR ± L-Asp Pred + VCR + DNR (once weekly) ± L-Asp	Pred + VCR + DNR + L-Asp	Pred + VCR	Pred + Cyt + VCR + DNR
Consolidation	MTX 15 mg/m² week	MTX 3 5-day courses	–	–	–	L-Asp 10 days	L-Asp 10 days
Maintenance	6-MP + MTX once weekly	MTX twice weekly	6-MP + MTX	6-MP + MTX or MTX	6-MP + MTX	6-MP + MTX	6-MP + MTX
Reinductions	Pred + VCR every 6 months or at 2, 4, 7, 11 months and every 6 months	Pred + VCR every 3 months	Pred + VCR + DNR at 1, 2, 4, 7, 11 months and every 6 months	Pred + VCR or Pred + VCR + DNR monthly for 6 months, every 3 months for 2 years and every 6 months	Pred + VCR + DNR + L-Asp at 1, 2, 4, 7, 11 months and every 6 months	Pred + VCR monthly for 6 months and every 3 months	Pred + Cyt + VCR + DNR + Ara-C monthly for 6 months, every 3 months for 1 year and every 6 months
IT MTX	at each reinduction	–	monthly	0 or monthly	weekly for 6 weeks and monthly		
Skull irradiation	–	–	–	–	–	+ in half of the patients	+

Pred: prednisone; VCR: vincristine; Cyt: cytoxan; DNR: daunorubicin; L-Asp: L-asparaginase; ara-C: cytosine arabinoside; 6-MP: 6-mercaptopurine; MTX: methotrexate

PBC count, and presence or absence of tumor: class 1: no poor prognostic factors; class 2: one poor prognostic factor; class 3: two or three poor prognostic factors. It may be argued that these prognostic factors are interrelated. However, in a previous study of 893 patients, age did not correlate with PBC count ($r = 0.005$) or with the presence or absence of tumor, the mean age being 13 years for patients without tumor masses and 11 for those with tumor. On the other hand there is admittedly a correlation between PBC count and the presence of tumor (mean PBC count in patients without tumor = 24,000 versus 89,000 in those with tumor). Keeping these restrictions in mind, the physician may nevertheless use this classification for a quick overall appraisal of his patient's prognosis.

Results

1. Rate of Complete Hematologic Remission (CHR)

Table 2 indicates the CHR rate according to age and treatment protocol. The data shown confirm what has long been known, namely that the response rate is lower in adults (1–15 age group VS > 15: $P < 0.01$). There is no significant difference between treatment protocols.

The CHR rate according to pretreatment PBC count is shown in Table 4. The difference between patients with a PBC count greater than 35,000 and those with one of less than 35,000 is statistically significant ($P < 0.0001$). Table 4 illustrates the differences in CHR rate between the three prognostic classes as defined above.

Analysis of treatment failures revealed that 50% of deaths resulted from aplasia (induction deaths) and 50% from blastic regeneration (resistance). The pattern of failure was the same in all treatment protocols but the severe toxicity of the combination of prednisone, vincristine, daunorubicin, and L-asparaginase in adults should be emphasized (Henderson and Glidewell, 1974).

2. Duration of CHR

Duration of CHR according to age is shown in Figure 1. It is shorter in patients less than 1 year or over 15 years old.

Shorter CHR is also seen in patients with an initial PBC count above 35,000/mm³ ($P < 0.0001$) (Fig. 2) and in those with tumor masses as against those without tumors ($P < 0.001$) (Fig. 3). The prognostic significance

Table 2. Rate of complete hematological remission according to age (between $> 1 < 15$ and 15, $P < 0.01$)

Age (years)	02-04 LA 64 ALGB 6601	06 LA 66	ALGB 6801	ALGB 7111	01 LA 69	01 LA 72	Total
< 1	2/2	6/6	1/1	4/5	1/1	1/1	15/16 94%
> 1 < 15	111/123 90%	82/83 99%	92/104 88%	99/108 92%	2/2 100%	42/44 95%	428/464 92%
> 15 < 20	11/14	7/10	9/10	9/12	1/1	8/9	45/56 80%
> 20	11/13	22/30 73%	–	–	16/24 67%	24/30 80%	73/97 75%
Exclusions[a] from protocol	5	2	6	3	1	–	17/650 2.6%
Total	135/152 88.8%	117/129 90.7%	102/115 88.7%	112/125 89.6%	20/28 71.4%	75/84 89.3%	561/633 88.6%

[a] Reasons for exclusion were early deaths before treatment or complete protocol violations

Table 3. Rate of complete hematological remission according to initial PBC (for all protocols between PBC $< 35 \times 10^3$ and $> 35 \times 10^3$, $P < 0.0001$)

PBC (mm^3)	02-04 LA 64 ALGB 6601	06 LA 66	ALGB 6801	ALGB 7111	01 LA 69	01 LA 72	Total
$< 35 \times 10^3$	103/108 95.4%	89/94 94.7%	67/70 96%	94/102 92%	9/13 69.2%	56/65 86%	418/452 92%
$\geqslant 35 \times 10^3$	32/44 73%	28/35 80%	35/45 78%	18/23 78%	11/15 73%	19/19 100%	143/181 79%
Total	135/152	117/129	102/135	112/125	20/28	75/84	561/633

Table 4. Rate of complete hematological remission according to prognostic classes (between class 1 and class 2, $P < 0.03$; between class 2 and class 3, $P < 0.002$)

	02-04 LA 64 ALGB 6601	06 LA 66	ALGB 6801	ALGB 7111	01 LA 69	01 LA 72	Total
Class 1	71/74 96%	48/49 98%	36/38 95%	52/55 95%	1/1 –	11/12 92%	219/229 95.5%
Class 2	43/48 90%	39/42 93%	34/36 94%	39/43 91%	3/5 60%	38/43 88%	196/217 90%
Class 3	21/30 72%	30/38 79%	32/41 78%	21/27 79%	16/22 73%	26/29 89%	146/187 78.6%

of PBC count applies to all age groups. Five infants less than 1 year old with an initial PBC count of less than 35,000 have had a CHR lasting at least 6 months, and two of them have now reached 48 months, whereas seven out of eight with a PBC exceeding 35,000 had a CHR lasting less than 9 months. It thus appears that the elevated PBC count often encountered in this age group plays an important, though not exclusive, role in the severe prognosis characteristic of this age group (Cangir et al., 1975).

Among patients aged 1–15 years old there was a highly significant difference according to whether the PBC count was above or below 35,000/mm^3, while in patients over 15 years of age the same tendency was seen though the difference was not significant, owing partly to the smaller number of patients and suggesting

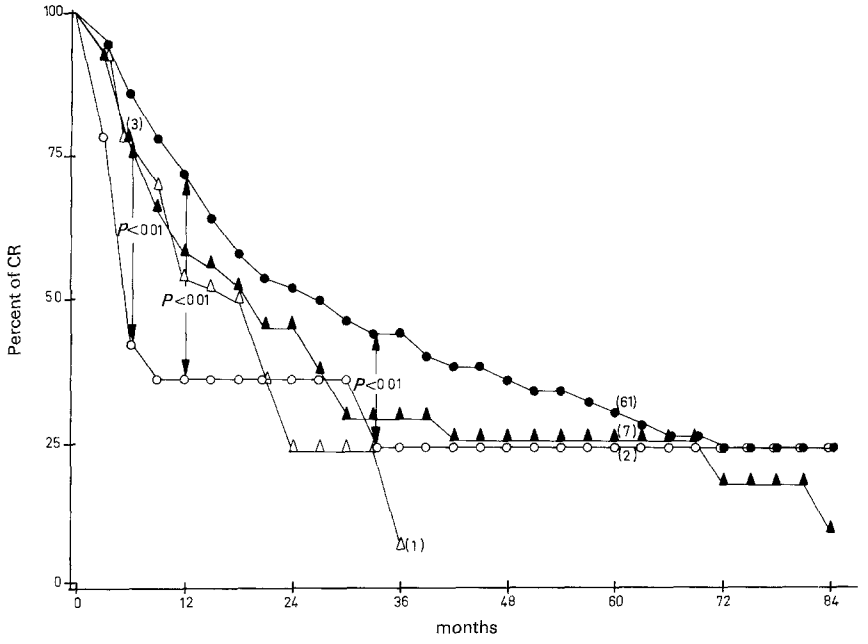

Fig. 1. Duration of CHR according to age. ○ < 1 (14 patients); ● > 1 < 15 (427 patients); △ > 15 < 20 (44 patients); ▲ > 20 (72 patients)

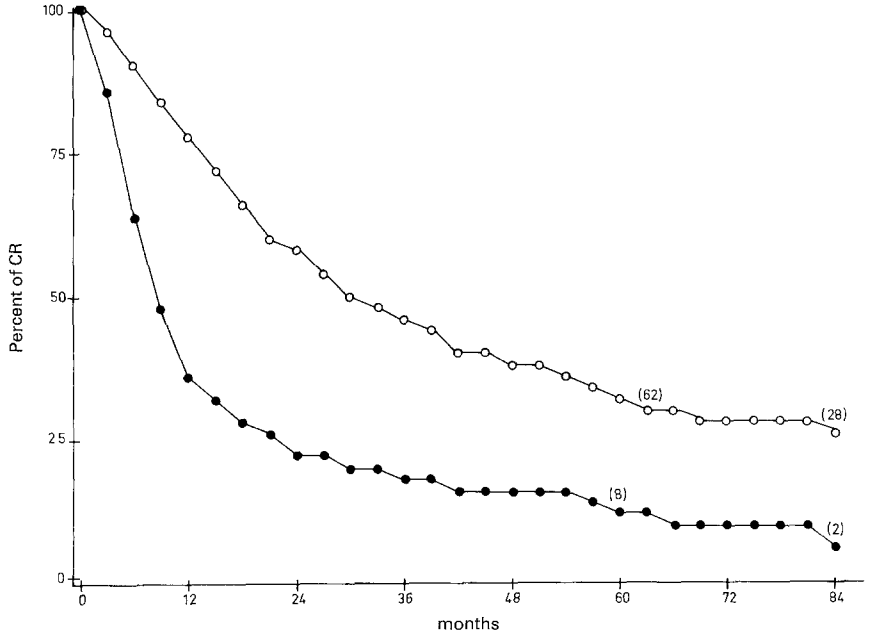

Fig. 2. Duration of CHR according to initial PBC ($P < 1/10^8$). ○ PBC < 35 × 10^3 (414 patients); ● PBC > 35 × 10^3 (143 patients)

that in this group age becomes the overriding factor, with a possible relationship to immunity and stem cell stores. Figure 4 shows the duration of CHR in the three prognostic classes. The difference is significant between classes 1 and 2 ($P < 0.05$) and between classes 2 and 3 ($P < 0.0001$).

Figure 5 illustrates the duration of CHR according to treatment protocols in patients between 1 and 15 years of age.

The best protocol, although the difference was not significant, appears to have been ALGB 7111, which included L-asparaginase for induction or consolidation, with reinduction courses every 3 months for 5 years. The steep decline observed in protocol 01 LA 72 may be ascribed to overspaced reinduction courses after the 12th month (every 6 months). Just how intense treatment should be is still an unsolved problem.

Differences between protocols were also observed in the other age groups: patients between 15 and 20 fared better with protocol 01 LA 72, with an 87% CHR rate at 18 months versus 25% with protocol 02, 04 LA 64. Those over the age of 20 had a higher CHR rate with protocol 01 LA 69, when daunorubicin was given for 3 consecutive days and combined with L-asparaginase,

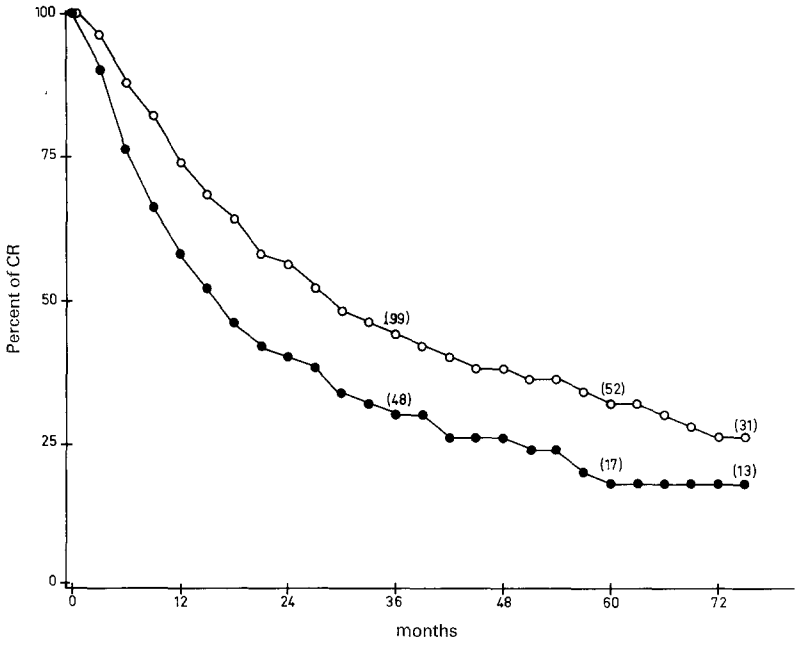

Fig. 3. Duration of CHR according to presence or absence of tumor ($P < 0.001$). ○ no tumors (315 patients); ● presence of tumors (239 patients); not known in three patients

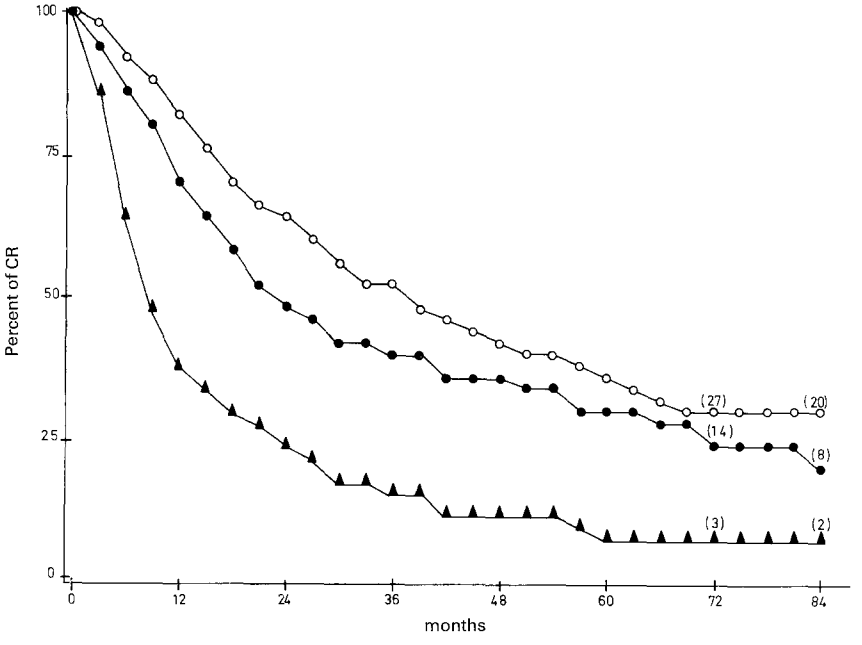

Fig. 4. Duration of CHR according to the prognosis classes. ○ class 1 (222 patients); ● class 2 (204 patients); ▲ class 3 (133 patients)

than with protocol 06 LA 66, when it was given once a week.

Improved treatment is illustrated by the fact that patients with less than 35,000 PBC/mm^3 had a 78% CHR rate at 18 months in 1972 versus 52% in 1964.

Improved results in treatment protocols suggest the need for adding other drugs to vincristine and prednisone in the induction or consolidation phase. More intensive therapy generally leads to earlier destruction of blasts and to earlier complete remission; thus induction toxicity may not be increased by a more aggressive initial treatment.

Table 5 shows the duration of CHR according to prognostic class and treatment protocol, and the influence of the former is clearly apparent.

3. Meningeal Relapse

The meningeal relapse rate (occurring as the initial relapse) according to age is shown in Figure 6. It can be seen that meningeal relapse is particularly common in infants less than 1 year old.

The rate of meningeal relapse is higher in patients

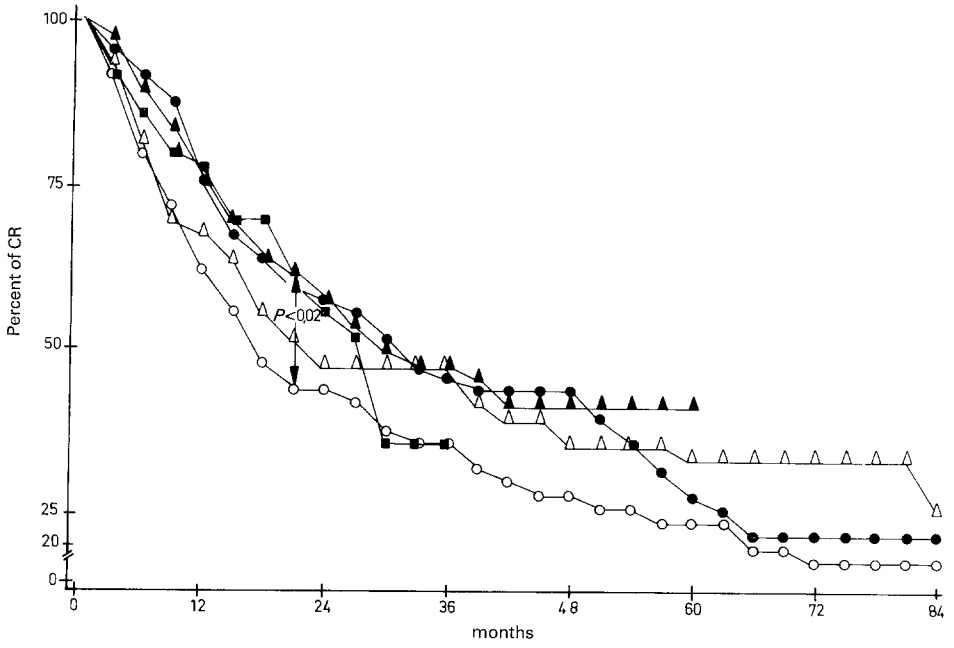

Fig. 5. Duration of CHR according to treatment in patients > 1 < 15 years. ○ 02–04 LA 64-ALGB 6601 (112 patients); ● 06 LA 66 (82 patients); △ ALGB 6801 (91 patients); ▲ ALGB 7111 (98 patients); ■ 01 LA 72 (42 patients)

Table 5. Rate of CHR at 1, 2, 3, 4 years according to prognostic class and protocol

	All cases	02-04, ALGB 6601	06 LA 66	ALGB 6801	ALGB 7111	01 LA 69	01 LA 72
Class 1							
% at 1 year	82 ± 5%	68 ± 12%	84 ± 11%	92 ± 10%	90 ± 8%	–	91 ± 17%
% at 2 years	64 ± 7%	53 ± 12%	64 ± 14%	72 ± 15%	69 ± 13%	–	76%
% at 3 years	51 ± 7%	39 ± 12%	50 ± 15%	68 ± 16%	56 ± 14%	–	–
% at 4 years	43 ± 7%	30 ± 12%	50 ± 15%	49 ± 18%	51 ± 14%	–	–
Class 2							
% at 1 year	70 ± 7%	57 ± 16%	64 ± 17%	72 ± 16%	75 ± 14%	80 ± 30%	80 ± 13%
% at 2 years	47 ± 8%	34 ± 16%	50 ± 18%	40 ± 18%	57 ± 17%	83 ± 30%	51 ± 18%
% at 3 years	52 ± 8%	32 ± 15%	37 ± 18%	40 ± 18%	47 ± 17%	83 ± 30%	–
% at 4 years	29 ± 8%	28 ± 15%	9 ± 12%	32 ± 17%	42 ± 18%	83 ± 30%	–
Class 3							
% at 1 year	38 ± 9%	32 ± 22%	34 ± 18%	30 ± 17%	39 ± 22%	67 ± 26%	44 ± 24%
% at 2 years	24 ± 8%	0%	21 ± 16%	15 ± 17%	34 ± 22%	67 ± 30%	25 ± 22%
% at 3 years	15 ± 8%	–	9 ± 11%	15 ± 15%	25 ± 22%	33 ± 30%	–
% at 4 years	8 ± 7%	–	9 ± 11%	15 ± 15%	17 ± 20%	22 ± 27%	–

with an initial PBC count exceeding 35,000/mm^3 than in those with initial counts of less than 35,000/mm^3 ($P < 10^{-8}$). A correlation also exists between meningeal relapse and presence of tumor masses at the time of the initial work-up ($P < 0.01$).

A lower incidence of meningeal involvement has been reported with earlier and more frequent use of intrathecal methotrexate (Jones) and skull irradiation (Simone et al., 1975), although neither of these procedures completely eliminates the risk (Bleyer et al., 1973; Duttera et al., 1973; Garwicz et al., 1975; Geiser et al., 1975; Gemon et al., 1973).

Meningeal prophylaxis may prove more effective if adjusted so as to take account of the risk factors mentioned, rather than being applied in an arbitrarily standard fashion. Indeed, in an earlier randomized study, skull irradiation plus intrathecal methotrexate was found to be more effective than intrathecal methotrexate alone in those patients with a high initial PBC count (B. Jones, personal communication).

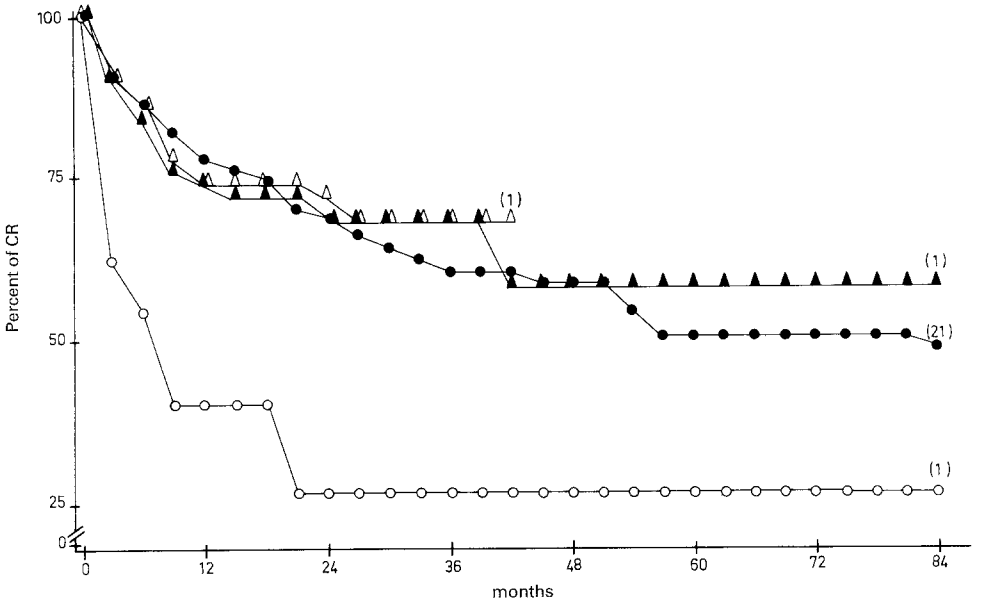

Fig. 6. Rate of initial meningeal relapse according to age. ○ < 1 year (14 patients); ● > 1 < 15 years (421 patients); △ > 15 < 20 years (44 patients); ▲ > 20 years (69 patients)

4. Testis Relapse

In our experience, when testis relapse is the initial manifestation of recurrence, it occurs later than meningeal relapse.

In the present study 24 cases were observed, to which 23 cases seen in patients not included among the 650 may be added. For these 23 patients the initial treatment was not given at Saint Louis but we treated them thereafter. Of these 47 cases of primary testicular relapse (PTR), 40 occurred alone, three had a concomitant meningeal relapse, and four were accompanied by hematologic relapse. 42 cases were encountered in children and five in adults. Ten patients had a PBC count above 35,000/mm^3 and 28 had tumor masses. Testis relapse occurred within 1 year of diagnosis in ten patients, with in between 1 and 2 years in 14, between 2 and 3 years in nine, and after more than 3 years in 11. The latest recorded PTR occurred 69 months after diagnosis.

5. Role of Cytology in the Prognosis of ALL

The prognosis value of cytological type has long been suspected in ALL and has recently been demonstrated (Flandrin et al., 1973; Jacquillat et al., 1973a; Mathé et al., 1971; Pantazopoulos and Sinks, 1974). In this study, cytologic subtypes were available for 216 patients. Prognosis was poorer in 37 patients whose blast cells were more than twice as large as small lymphocytes with considerable variation in cell size, nuclear chromatin, nucleoli, and variable though often abundant cytoplasm (L2) than it was in 179 patients with smaller cells without nucleoli and with scanty cytoplasm (L1). There is controversy about the prognostic significance of lymphoblast size (Pantazopoulos and Sinks, 1974; Murphy et al., 1975; Oster et al., 1976). Our definition of L2 also includes qualitative features such as the presence of nucleoli, the degree of basophilia, and the population homogeneity or heterogeneity. Combining size and number of nucleoli, Lee et al. (1976) confirmed the impaired prognosis of large cells with nucleoli. In our hands the PAS value has no prognostic significance, in agreement with some authors (Shaw et al., 1977; Bennett and Henderson, 1969; Humphrey et al., 1974), and in disagreement with others (Ascari et al., 1975; Feldges et al., 1974; Vowels and Willoughby, 1973).

ALL has been subdivided immunologically on the basis of membrane immunoglobin studies, IgG aggregates, E-rosette formation and cytotoxic activity of anti-T and anti-B serum (Brouet et al., 1976; Greaves et al., 1975; Haegert et al., 1975). B-cell markers are found in peculiar types of ALL where the cells resemble those of Burkitt's lymphoma. Such cases are rare and survival is shorter, owing essentially to resistance to therapy.

Of 100 patients assayed by J. C. Brouet, using a previously described technique (Brouet et al., 1976), 28 were found to have T-cell markers. These patients presented more frequently with a high PBC count (52%; $P < 0.0005$) and tumor masses (52%; $P < 0.01$). Six of these patients had thymic infiltration. In the non-T

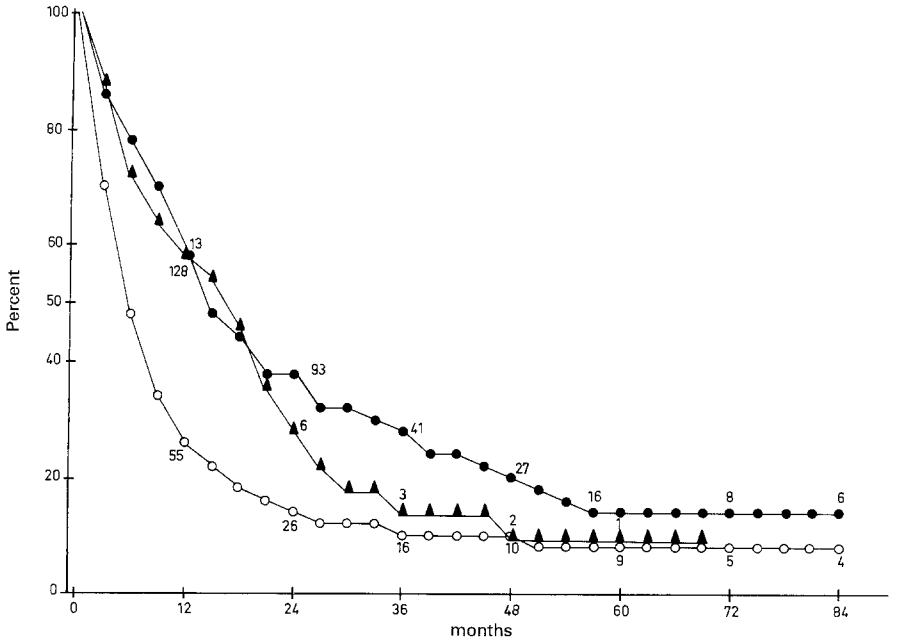

Fig. 7. Survival after first relapse according to site. ○ first hematological relapse (240 patients); ● first meningeal relapse (166 patients); ▲ first testicular relapse (25 patients)

Table 6. Deaths in CR according to age and treatment protocol

Age	02-04 LA 64 ALGB 6601	06 LA 66	ALGB 6801	ALGB 7111	01 LA 69	01 LA 72	Total
< 1	0/2	0/6	0/1	0/4	0/1	0/1	0/15
> 1 < 15	7/111 6%	7/82 8%	8/92 8%	1/99 1%	1/3	7/24 16%	31/429 7.2%
> 15 < 20	1/11 9%	0/7	1/9 11%	0/9	0/1	1/8 12%	3/45 6.6%
> 20	1/11 9%	5/22 22%	—	—	2/16 12%	1/24 5%	9/73 12.3%
Total	9/135 6%	12/117 10%	9/102 8%	1/112 1%	3/20 15%	9/75 12%	43/561 7.6%

group, consisting of 69 null-cell ALL and three B-cell Burkitt-type ALL, there were only one case of thymic infiltration and two cases of interbronchial node involvement. Leukemic meningitis supervened in five of the 28 cases of T-cell ALL as against only two of the 69 cases of null ALL. As for observations that non-B, non-T lymphoblasts react with anti-CLL sera and contain a terminal deoxy-nucleotidyl transferase (McCaffrey et al., 1975), their prognostic significance in ALL remains to be assessed.

6. *Survival*

Survival is chiefly dependent on the length of the first CHR (Jacquillat et al., 1973c). Survival after relapse is almost equally short, whether the first relapse is hematological, meningeal, or testicular (Fig. 7). Treatment of hematological relapses often results in complete remission (75% with Ara-C, cyclophosphamide, and daunorubicin). These remissions are usually short-lived, however (median 7 months), except in patients who have been inadequately treated during induction.

To date, meningeal relapses have been treated by intrathecal methotrexate and skull irradiation in previously nonirradiated patients. Testicular relapses have been managed by bilateral irradiation without modification of systemic therapy. Whether systemic therapy should be modified or not remains an open question, which we are currently investigating.

The mortality rate of patients in complete remission, reflecting the toxicity of therapy, is shown in Table 6 for

the various age groups and treatment protocols. It may be remarked that toxicity increases with an increasing number of drugs, and that for a given protocol toxicity tends to be more severe in older patients. The problem of when to discontinue treatment is still unsolved. 115 patients have had their treatment stopped and 43 have had a recurrence, all before 33 months. CHR is continuing in 55% of these patients, with a follow-up of 6 to 84 months and some may well be cured.

The breakdown of this population of 115 patients was as follows:

1. 36 patients were treated for less than 1 year (usually 8 months). Recurrence has occurred in 26 patients, before the 6th month in 18, within 6 months to 1 year in six, and with in 1–2 years in two. Ten patients are still in remission, eight with a follow-up exceeding 6 years. Recently one of these patients relapsed after 7 years of unmaintained remission.

2. Nine patients had their treatment stopped after 1–2 years. Of these, four have relapsed, two after 6 months and two after 21 months. The follow-up of the five remaining patients is 36–78 months.

3. Ten patients had treatment discontinued after 2–3 years: there have been two recurrences at 3 and 9 months; follow-up of the eight patients in CHR is now 24–84 months.

4. Six patients had treatment stopped after 3–4 years. Two have relapsed (6 and 12 months) and the follow-up is currently 6, 21, 39, and 84 months for the other four patients.

5. There were 32 patients treated for 4–5 years. Of these eight have had a recurrence (6 during the first year, 1 at 18 months, and 1 at 30 months). The 24 patients in CHR have a follow-up of 9–84 months.

6. There were 22 patients treated for more than 5 years. Only one of these patients has had a recurrence (30 months after discontinuation of treatment). The 21 remaining patients have a follow-up of 6–54 months (mean = 36 months).

The predictive factors for late relapses are still unknown. The guarantee time, namely the time after which no relapse occurs, may vary from protocol to protocol; it is 9 years according to Izawa et al. (1977).

Although long-term remissions are more frequent in females and late relapses are more frequent in males, neither difference is statistically significant in our experience. The negative influence of testicular relapse (Baum et al., 1977) is increasing since prophylaxis has lowered the rate of occurrence of meningitis.

Discussion

We have stated that current treatment modalities have improved remission rates and survival in all types of ALL but that besides treatment, differences persist according to several prognostic factors. These factors are not absolute and patients with a favorable profile may have short survival and vice versa for other reasons. Nevertheless, these prognostic factors raise the question of the rationality of standard treatment for all ALL patients. Should prognostic factors be used solely for the purpose of final analysis (Karon et al., 1975) of the results of any given treatment? One can legitimately ask whether this does not result in overtreatment of some patients and undertreatment of others. Would it be unreasonable to classify patients on the basis of prognostic factors and restrict the use of the more aggressive modalities to patients with a poorer outlook, for example those with a high PBC count and/or tumor masses?

As for the optimal duration of treatment, until a circulating marker of persistent minimal active disease becomes available, the decision to discontinue treatment will remain a difficult one. The plateau of the survival curves suggests that some cases of ALL may be actually cured. Do they indicate when treatment may be safely discontinued? No significant difference was noted in patients whose treatment was continued or discontinued beyond 42 months (Aur et al., 1974) or 5 years (O. Glidewell and J. F. Holland, personal communication). Randomized studies may help to answer this question.

In conclusion, we feel that well-defined prognostic factors are of use and should be taken into account in the search for an assessment of improved treatment modalities. Ultimately it may be hoped that more effective treatment will become available, enabling us to do without these prognostic factors.

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