The Effect of 6-Mercaptopurine on the Duration of Steroid-induced Remissions in Acute Leukemia: A Model for Evaluation of Other Potentially Useful Therapy

From the ACUTE LEUKEMIA GROUP B

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THE EXISTENCE of effective palliative therapy for acute leukemia has hampered the evaluation of new and potentially more effective therapeutic agents. Therapeutic trials with new agents are usually reserved for patients who have been treated with and have become refractory to the agents of proven value. Such patients have active acute leukemia at the onset of study. Because agents are studied for their ability to induce remissions and are not always effective, many patients expire during treatment and thus the number of patients that can receive a new agent is greatly diminished. Moreover, the study of the therapeutic and toxic effects of agents in such patients is frequently confused by the manifestations of the active leukemic process.

To overcome these problems, a study was designed to test the ability of a therapy to prolong the duration of a remission. A higher proportion of patients would be available early in the course of their illness for such a study. Moreover, the treatment of patients in whom the leukemic process is in remission would permit objective evaluation of pharmacologic and toxic properties of the agent. Finally, a study of remission maintenance uses a continuous variable, namely duration of remission compared to remission induction where a yes or no variable is used, and allows for the quantitative evaluation of an agent. Such a quantitative evaluation could be a basis for ranking of agents in man. This ranking could be of great aid to those concerned with the synthesis of new compounds and the testing of compounds in animal systems.

6-MP was selected as a known active agent to test such an experimental design. An abstract of this study has been presented previously.[1]

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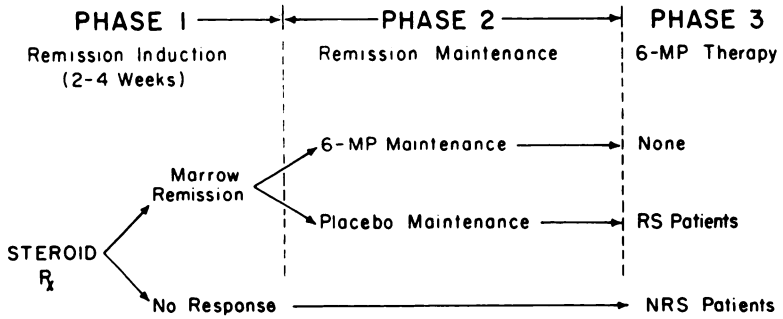

Fig. 1.—Design of the study.

Methods

A protocol* was prepared for the study. The experimental design is outlined in figure 1. The adrenal corticosteroids result in the highest rate of remission induction of the currently available therapeutic agents.[2-4] Moreover, these remissions are relatively short and are usually not prolonged significantly by maintenance corticosteroid therapy.[2,3,5] Prednisone was selected as the corticosteroid used for the remission induction phase of the study (Phase I). The dosage was 40 mg. per square meter of body surface area[6] per day divided into two or three equal oral doses.

Because corticosteroids are primarily active against acute lymphocytic leukemia of childhood,[2,3,7] the study was confined to patients under the age of 20 years. All such patients with proven acute leukemia who were admitted to the participating institutions and who had received no chemotherapy prior to admission were entered into the study.

In Phase I, corticosteroid therapy was continued until complete bone marrow remission was achieved (A-1)† or for a maximum of 28 days. Patients who failed to show marrow improvement (from A-3) after 28 days of corticosteroid therapy were given 6-MP as their next course of therapy for remission induction (Phase III, NRS patients).‡ Patients with marrow remission (A-1) before 28 days or marrow remission (A-1 or A-2) on the 28th day were assigned randomly to 6-MP or placebo (given double-blind) for the remission maintenance phase of the study (Phase II). This part of the study was designed for sequential evaluation so that the study could be stopped as soon as it was established that one treatment was superior to the other in the maintenance of remissions. The sequential design is explained in the Appendix.

Full dosage of 6-MP (3 mg./Kg./day) was used for maintenance therapy unless toxicity modified dose.[9] Placebo was given at the same dose. Maintenance therapy was continued in Phase II until bone marrow relapse occurred (A-3). At this time, an envelope was opened and those patients who had received placebo maintenance were treated with 6-MP for remission induction and maintenance (Phase III, RS patients). Those who had received 6-MP maintenance went off study. Technic of case evaluation and of 6-MP therapy have been previously described.[9]

Results

A total of 97 patients with acute leukemia were entered into the study by the 11 participating institutions. Of these patients, 92 (95 per cent) were

*Protocol No. 3 of the Acute Leukemia Group B may be obtained from the Cancer Chemotherapy National Service Center, National Cancer Institute, Bethesda, Md.

†Criteria for response to therapy are explained in reference 8.

‡This phase of study was designated Phase III, since these patients were in the remission maintenance phase (Phase II) for zero time.

Table 1.—*Number of Patients Entered on Study and Accepted for Analysis, by Institution*

Institution	No. Entered	No. Accepted for Analysis
1. Children's Hospital of Philadelphia	27	25
2. National Cancer Institute	18	18
3. Mayo Clinic	16	15
4. Roswell Park Memorial Institute	12	12
5. Medical College of Virginia	4	4
6. Emory University	4	4
7. Bowman Gray School of Medicine	4	3
8. Hitchcock Hospital	3	3
9. Jefferson Medical College Hospital	3	3
10. Mount Sinai Hospital (New York)	3	3
11. Maimonides Hospital (Brooklyn, N. Y.)	2	2
	97	92

Table 2.—*Patients Classified by Response in Phase I (Randomization Category) and Best Response in Phase I and II*

Response in Phase I		Best Response in Phase I and II	
Randomization category	No. of patients (%)	Complete remission	Partial remission
A-1 marrow, placebo	24 (26%)	24	0
A-1 marrow, 6-MP	24 (26%)	23	1
A-2 marrow, placebo	5 (5%)	3	2
A-2 marrow, 6-MP	9 (10%)	5	4
No response	30 (33%)	0	0
All patients	92	55 (60%)	7 (7%)

considered acceptable for analysis. These are given by institution in table 1. The other five (5 per cent) patients were rejected for the following reasons: two had different treatment administered in Phase I, one had no bone marrow at end of Phase I, one had drug error, and one was lost to follow-up in Phase I.

The first patient was entered in April 1959 and the last one in April 1960. The decision to terminate the study was based on the analysis of the duration of remissions of 21 pairs of patients—this number resulting in the sample path crossing a boundary line of the restricted sequential procedure. The sequential design is explained in the Appendix.

Remission Induction with Prednisone (Phase I)

The responses to prednisone therapy are given in table 2. Of the 92 patients, 62 (67 per cent) had improved to complete or partial remission marrow (A-1 or A-2) after 28 days of steroid therapy. Forty-eight patients achieved complete remission marrows (A-1) and all but one of these went on to develop complete clinical and hematologic remission in Phase II (A-1, B-1, C-1, D-1). Of the 14 patients with partial remission marrows (A-2) on day 28, eight (57 per cent) went on to develop complete remissions in Phase II. This happened proportionately as often for patients receiving placebo in Phase II as

Table 3.—*Response to Steroids for Patients Classified by Initial Status*

Initial Status		No. of Patients	Complete and Partial Remissions Number (per cent)
Age (years)			
0–4		44	30 (68)
5–9		25	19 (76)
10–14		14	11 (78)
15–19		9	2 (22)
Type			
lymphocytic		72	54 (75)
myelocytic		13	3 (23)
unclassified		7	5 (71)
Symptoms to diagnosis (wks.)			
0–1		13	8 (62)
2–3		28	18 (64)
4–5		25	15 (60)
6–7		13	11 (85)
8 and over		13	11 (85)
Starting WBC			
below 5,000		27	22 (81)
5,000–9,999		23	18 (78)
10,000–19,999		9	6 (67)
20,000–49,999		17	9 (53)
50,000 and over		16	8 (50)
Starting platelet count			
under 25,000		30	17 (57)
25,000–49,999		33	22 (67)
50,000–99,999		14	11 (79)
100,000 and over		13	12 (92)
Platelets	*No. of blasts*		
under 30,000	under 5,000	17	13 (76)
	5,000 and over	16	4 (25)
30,000 and over	under 5,000	38	30 (79)
	5,000 and over	9	6 (67)

for patients receiving 6-MP in Phase II and hence probably was a result of the corticosteroid therapy. Thus, 60 per cent of the patients went into complete remission and 7 per cent into partial remission with Phase I corticosteroid therapy.

The response to corticosteroid therapy in patients classified by initial status is given in table 3. The percentage of remissions in the age group 15–19 was significantly lower than that in the younger age groups (prob. $\chi^2 < .01$). Those with myelocytic leukemia had a significantly lower frequency of remission than patients classified lymphocytic or unclassified (prob. $\chi^2 < .01$). These factors were related, i.e., myelocytic leukemia was more common in the age group 15–19 (four patients out of nine) than in the total group. Thus, of the 79 patients with acute lymphocytic or unclassified leukemia, 75 per cent developed complete or partial remissions with corticosteroid therapy. This figure was 78 per cent for the 67 patients with lymphocytic leukemia under age 15. When patients were classified by time from onset of symptoms to diag-

Table 4.—*Comparability of Patients Receiving 6-MP and Placebo (Numbers in Parentheses are Percentages)*

Factor	6-MP	Placebo
Age (yrs.)		
0–4	19 (58)	11 (38)
5–9	8 (24)	11 (38)
10–14	5 (15)	6 (20)
15 and over	1 (1)	1 (3)
Sex		
Male	20 (61)	17 (59)
Female	13 (39)	12 (41)
Type		
Lymphocytic	29 (88)	25 (86)
Myelocytic	0 (0)	3 (10)
Unclassified	4 (12)	1 (3)
Starting WBC		
Below 5,000	16 (48)	12 (41)
5,000–19,999	9 (27)	9 (31)
20,000–49,999	5 (15)	3 (10)
50,000 and over	3 (9)	5 (17)
Time from symptoms to diagnosis (wks.)		
0–4	20 (61)	15 (52)
5–9	10 (30)	12 (41)
10 and over	3 (9)	2 (7)

nosis, the frequency of remission was higher in those with 6 or more weeks duration, though the difference was not statistically significant (prob. $\chi^2 > .3$). When patients were divided by initial white blood count, there is evidence that the response rate decreased linearly with increasing white blood count (prob. $\chi^2 < .01$). For patients classed by platelet count, there was also evidence of a linear trend in response rate; the higher the platelet count, the higher the probability of responding to steroids (prob. $\chi^2 < .02$). When the patients were classed according to initial platelet count and number of blasts, those with a platelet count below 30,000 and a blast count above 5,000 had a significantly lower response rate of only 25 per cent, whereas the others had a response rate of about 75 per cent (prob. $\chi^2 < .01$).

Remission Maintenance with 6-Mercaptopurine and Placebo (Phase II)

Those patients who received 6-MP and those who received placebo are compared for a number of factors known to be associated with response to therapy[10] or survival[11] in table 4. There are no important differences between the 6-MP and placebo patients.

The lengths of the complete remissions for patients maintained on placebo and 6-MP therapy are compared in figure 2. There is a marked difference in the two remission curves. For patients maintained on 6-MP the median length of complete remission was 33 weeks; for those maintained on placebo, only 9 weeks. After 10 weeks of therapy, all patients receiving 6-MP were still in remission, whereas only 40 per cent of the patients receiving placebo were still in remission.

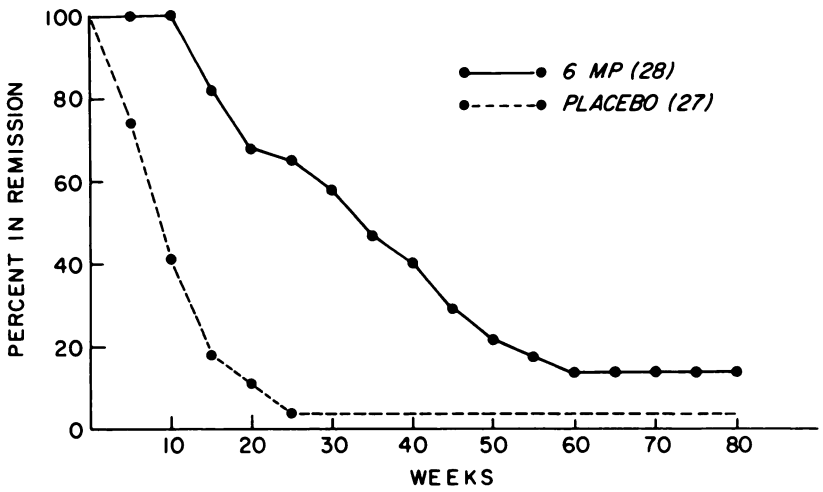

Fig. 2.—Effect of 6-MP and placebo maintenance therapy on the duration of complete remissions in Phase II.

There were seven patients in partial remission. Five received 6-MP maintenance and two received placebo. The lengths of remissions were as follows: 6-MP: 4, 6, 7, 15, 27 weeks; placebo: 4, 5 weeks. It appears that partial remissions are shorter than complete remissions, but the number of patients is too small to make any definitive statement.

The dose of drug was modified (either reduced to one-half, one-quarter or stopped) for 21 (64 per cent) of the 33 patients receiving 6-MP and for one patient (3 per cent) of the 29 receiving placebo. The reasons for drug modification are given in table 5. Hematologic toxicity was the most common reason for stopping drug. This occurred in 11 patients receiving 6-MP and one receiving placebo.

In table 6, the number and percentage of patients in remission having less than the median remission time is given by the initial status of the patient. If the true median remission time is the same for all patients in a category, say age, then it would be expected that 50 per cent of the patients in each sub-group would have remission times less than the median. Patients receiving 6-MP and placebo were included in the table. Those receiving 6-MP were classified using the 6-MP median remission time, and those receiving placebo according to the placebo median remission time. There is evidence that remissions are longer for those patients with longer intervals between

Table 5.—*Reasons for Drug Modification in Phase II for 6-MP and Placebo Maintained Patients*

	6-MP (33)	Placebo (29)
Hematologic	18	1
Gastrointestinal	7	0
	25*	1

*Four patients had hematologic and gastrointestinal toxicity.

Table 6.—*Effect of Initial Status on Duration of Remission in Phase II*

Initial Status		Number of Patients*	Number (per cent) Remitting Less than Median Remission Time†
Age (yrs.)			
0–4		28	12 (43)
5–9		18	8 (44)
10–14		11	8 (73)
15–19		2	1 (50)
Type			
lymphocytic		52	26 (51)
myelocytic		2	1 (50)
unclassified		5	1 (20)
Symptoms to diagnosis (wks.)			
0–3		23	15 (65)
4–7		25	12 (48)
8 and over		11	2 (18)
Starting WBC			
below 5,000		21	7 (33)
5,000–19,999		24	10 (42)
20,000 and over		14	12 (86)
*Platelets**			
under 25,000		15	9 (60)
25,000–99,999		32	13 (41)
100,000 and over		11	6 (55)
Platelets	*No. of blasts*		
under 30,000	under 5,000	13	7 (54)
	5,000 and over	4	3 (75)
30,000 and over	under 5,000	27	10 (37)
	5,000 and over	6	5 (83)

*Total number of patients in each category should be 59, since three patients on placebo had remission times equal to the median. Where total differs from this, it is because data were unavailable.

†Median remission time (complete and partial) for 6-MP patients = 29 weeks; median remission time (complete and partial) for placebo patients = 8 weeks.

symptoms and diagnosis and for those with low initial white blood counts. A χ^2 test indicates that the trend is linear in each case (prob. $\chi^2 < .01$). There is no evidence from these data that length of remission is related to age, type of leukemia, initial platelet count or number of blasts.

Response to 6-MP Therapy (Phase III)

The patients who did not respond to steroids in Phase I (designated NRS patients) and the patients responding to steroids and relapsing from remission on placebo in Phase II (designated RS patients) both received 6-MP as their next course of treatment. (Phase III). The percentages of responses (table 7) do not differ for the two groups of patients (prob. $\chi^2 > .70$), indicating that the subsequent response of a patient to 6-MP is independent of his prior response to corticosteroid therapy. The NRS patients and RS patients were compared for a number of prognostic factors at the start of Phase III. These prognostic factors were: white blood count, platelet count, percentage of

Table 7.—*Response to 6-MP in Phase III for Patients not Responding to Steroids (NRS) and Patients Responding to Steroids and Relapsing on Placebo (RS)*

Response	Non-Responders to Steroids (NRS)	Responders to Steroids: Patients relapsing on placebo (RS)
Complete remission	7 (33%)	9 (35%)
Partial remission	3 (26%)	7 (15%)
Remission (steroid)	2 (11%)	3 (10%)
No response	8 (30%)	8 (40%)
	20* (100%)	27† (100%)

*Ten of the 30 patients not responding in Phase 1 died in Phase 1.

†Two of the 29 patients maintained on placebo did not receive 6-MP as next course of treatment.

blasts, and hemoglobin. There were no important differences between the two groups of patients in the distribution of these factors.

The over-all response rate (CR + PR) of 55 per cent in the combined group of patients does not differ substantially from the 48 per cent response rate reported previously for 6-MP therapy.[7] The median complete remission time with 6-MP was 21 weeks for NRS patients (table 8a) and 17 weeks for RS patients (table 8b). The difference between the medians is not statistically significant (prob. $\chi^2 > .7$). The median complete remission time of 19 weeks for both groups of patients combined (16 patients) was somewhat shorter than the 33-week remission time for the 28 patients with complete remissions induced by steroid and maintained on 6-MP (Phase II). However, the latter patients started 6-MP therapy after they were in remission, while in Phase III 6-MP therapy was given to induce remission as well as to maintain it. The total exposure time to 6-MP was 28 weeks for the 16 NRS and RS patients in Phase III which is similar to the 33 weeks for 6-MP therapy in Phase II. Moreover, the total exposure to 6-MP for patients having complete and partial remissions in Phase III was similar to the duration of remissions in Phase II when 6-MP maintenance therapy was used (fig. 3). This indicates that the duration of effective 6-MP therapy is similar for either maintenance of a steroid-induced remission or for induction and maintenance of remission.

The duration of the 6-MP induced remissions for RS patients (Phase III) could be compared to the lengths of remissions on placebo (Phase II) for each patient (table 8b). Only two of the 19 remissions were shorter when the remission was maintained on 6-MP. The mean difference of 3.8 weeks favoring 6-MP maintenance represents a statistically significant increase in remission time (prob. $t < .05$). This indicates that an experimental design utilizing each patient as his own control would have revealed that 6-MP could maintain remissions longer than placebo.

Survival of Patients

Survival curves dated from the start of Phase II are given in figure 4. Phase II began after 28 days of prednisone therapy or the date of the first A-1 mar-

Table 8a.—*Lengths of Remissions Induced by 6-MP for Non-Responders to Steroids (NRS Patients)*

(NRS Patients)	Weeks	Median (weeks)
Complete remission (7):	14,15,18,21,37,57,74	21
Partial remission (3):	1,14,18	14
Remission (steroids) (2):	43,51	47

Table 8b.—*Lengths of Remissions for Patients Responding to Steroids (RS Patients)*

	Length of Remission on 6-MP Phase III (wks.)	Length of Remission on Placebo Phase II (wks.)	Difference (wks.)	
	CR, 8	CR, 24	−16	
	CR, 8	CR, 8	0	
	CR, 14	CR, 12	2	
Median CR =	CR, 17	CR, 8	9	
17 wks.	CR, 17	CR, 17	0	
	CR, 20	CR, 18	2	
	CR, 20	CR, 12	8	
	CR, 26	CR, 9	17	
	CR, 33	CR, 13	20	
	PR, 3	CR, 1	2	Mean diff. =
	PR, 6	CR, 7	−1	3.8 weeks
Median PR =	PR, 7	CR, 4	3	s = 7.3 weeks
10 wks.	PR, 9	PR, 4	5	
	PR, 10	CR, 6	4	
	PR, 10	CR, 7	3	
	PR, 12	PR, 5	7	
Median R(S) =	R(S), 5	CR, 2	3	
12 wks.	R(S), 12	CR, 12	0	
	R(S), 13	CR, 8	5	

row, whichever was earlier. For 6-MP-treated patients the median survival time was 54 weeks and for placebo patients 44 weeks. The difference between the median survival times is not significant (prob. $\chi^2 > .2$), though the curve for 6-MP patients is always above that for placebo patients. Thus, although 6-MP therapy gave longer remissions than placebo therapy, the fact that placebo patients were treated subsequently with 6-MP compensates for this so that survival did not differ significantly for the two groups.

When survival was dated from the start of Phase I, the median survival times were: 6-MP, 60 weeks; placebo, 46 weeks; non-randomized, 16.5 weeks (fig. 5). Again, the difference in the medians is not statistically significant between 6-MP and placebo patients (prob. $\chi^2 > .3$), but the non-randomized patients survived a significantly shorter period than either of the other groups of patients (prob. $\chi^2 < .05$). This resulted primarily from 10 deaths during Phase I therapy among those patients not responding to steroid therapy.

In figure 6 the survival curve of those patients not responding to steroids in Phase I (NRS patients) is compared to the survival curve of patients responding to steroids and relapsing on placebo maintenance (RS patients).

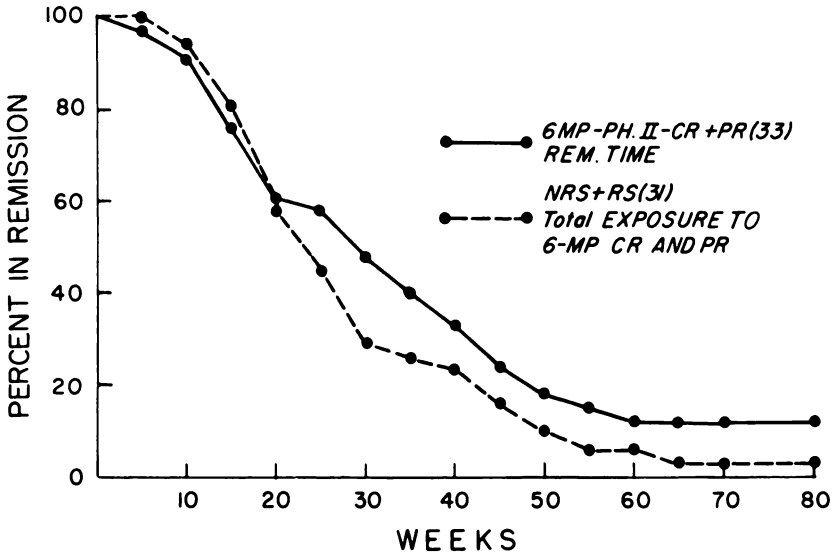

Fig. 3.—Duration of 6-MP therapy in Phase II and in Phase III. Duration of complete and partial remissions for 33 patients receiving 6-MP maintenance therapy (Phase II), compared with duration of 6-MP induction and maintenance therapy for 31 NRS and RS patients who responded to 6-MP remission induction therapy (Phase III).

The survival for both groups of patients is dated from the start of 6-MP therapy in Phase III. There is effectively no difference between the curves. Consequently, there is no evidence that prior response to steroids influences later survival of the patient.

In table 9 the number and percentage of patients surviving less than the median survival time is given for patients classified by initial status. All patients entering study were included and the survival of each was compared to the median survival time of his group, *viz.*, 6-MP-maintained (60 weeks), placebo-maintained (46 weeks) and non-randomized (16.5 weeks). There is evidence of a linear trend in the percentages for patients classed by starting white blood count and time from symptoms to diagnosis (prob. $\chi^2 < .05$, prob. $\chi^2 < .001$, respectively). The higher the starting white blood count or the shorter the time from symptoms to diagnosis, the poorer the survival time. There is no evidence from these data that median survival time (after adjustment for response in Phase I and maintenance therapy) is related to age (up to 20 years), type of leukemia or starting platelet count.

Remission Induction vs. Remission Maintenance

A question can be raised: "Do remission induction clinical trials test the same hypothesis as remission maintenance trials?" Or, phrased another way, "Is the percentage of patients in relapse who will respond to an agent the same as the percentage of patients in remission who will have their remission prolonged in a remission duration trial?"

In this study, we can test the hypothesis that the percentage of patients

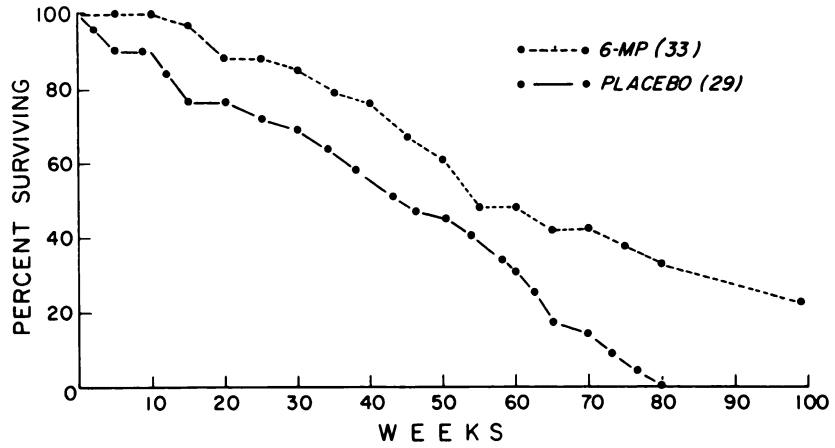

Fig. 4.—Survival from start of Phase II treatment to death.

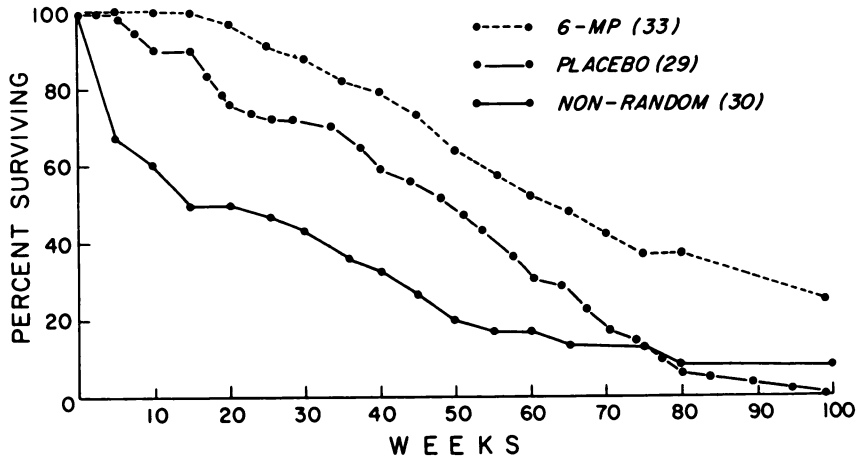

Fig. 5.—Survival from start of Phase I treatment to death.

responding to 6-MP is the same as the percentage of patients having prolonged remissions as a result of 6-MP maintenance. In figure 7, three remission curves are presented; one for the 6-MP-maintained patients in Phase II, one for placebo-maintained patients in Phase II and an "adjusted" placebo remission curve. The adjustment to the placebo remission curve was made by substituting the total exposure times to 6-MP (remission induction time + remission duration time) for placebo patients responding to 6-MP in Phase III and by using the placebo remission times for patients not having a later response to 6-MP. If the percentage of patients in the placebo group showing a later response to 6-MP is the same as the percentage of patients in the 6-MP group having prolonged remissions, the adjustment would bring the placebo curve close to the 6-MP curve. (It has previously been established that the lengths of 6-MP-maintained remissions in Phase II and III are not different.) There is still a substantial difference between the two curves—suggesting

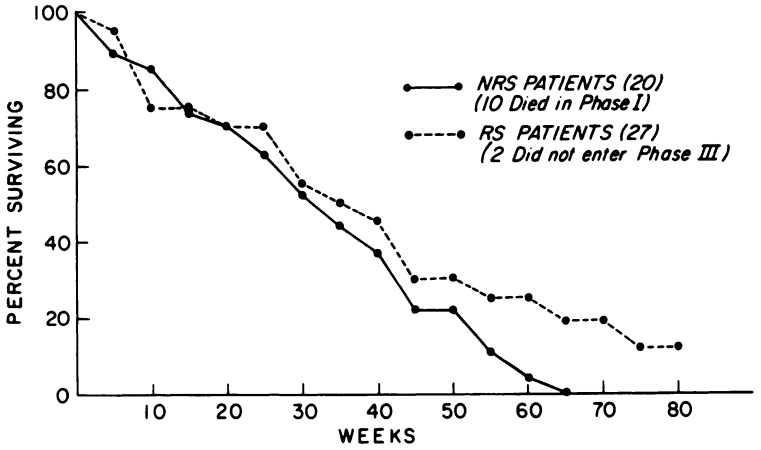

Fig. 6.—Survival from start of Phase III treatment to death. Comparison of patients who had responded to steroid therapy (RS) and patients who had not responded to steroid therapy (NRS).

that a higher percentage of patients have prolonged remissions as a result of 6-MP maintenance than respond to 6-MP in a remission-induction trial.

Discussion

The antileukemic activity of 6-mercaptopurine was clearly demonstrated by its ability to prolong a corticosteroid-induced remission. This should be an effective experimental design for the study of new agents. Corticosteroid therapy can induce remissions in almost 80 per cent of patients under age 15 with acute lymphocytic leukemia. Thus nearly all patients with this disease are available for the study of new agents. For patients with acute myelocytic leukemia, corticosteroids are not effective for remission induction,[7] but it is possible that other active compounds such as 6-MP or methylglyoxal-bis-guanylhydrazone[12] could be used, followed by studies of remission maintenance with a new agent. Although the frequency of response to corticosteroids is high, the prognosis for the patients who fail to respond is poor (30 per cent mortality in 4 weeks). It may be useful for future studies to use a combination of steroids plus another active drug such as 6-MP in an attempt to increase the fraction of patients entering remission with initial therapy.

This experimental design permits study of a new agent in a relatively uniform group of patients, all of whom have had remission induced by adrenal corticosteroids and who have had no other chemotherapy. This avoids the potential problem of alteration of tumor behavior as a result of previous therapy (conditioned tumor), and also avoids the use of adjuvant corticosteroid therapy which often complicates the study of new agents in patients with active acute leukemia. The treatment of patients in their first remission permits evaluation of drug effect and toxicity without complication by the manifold biological effects which result from active acute leukemia. Moreover, because the patients are in remission, their treatment is not complicated by other supportive therapy, such as transfusions, antibiotics, etc.

Table 9.—*Effect of Initial Status on Survival*

Initial Status		Number of Patients*	Number (per cent) Surviving Less than Median Survival Time†
Age			
0–4		43	21 (49)
5–9		25	10 (40)
10–14		13	9 (69)
15–19		9	5 (56)
Type			
lymphocytic		70	34 (49)
myelocytic		13	8 (62)
unclassified		7	3 (43)
Symptoms to diagnosis (wks.)			
0–3		40	24 (60)
4–7		37	18 (49)
8 and over		13	3 (23)
Starting WBC			
below 5,000		25	8 (32)
5,000–19,999		32	15 (47)
20,000 and over		33	22 (67)
*Platelets**			
Under 25,000		29	13 (45)
25,000–99,999		46	22 (48)
100,000 and over		13	9 (69)
*Platelets**	*No. of blasts*		
under 30,000	under 5,000	16	6 (38)
	5,000 and over	16	9 (56)
30,000 and over	under 5,000	37	17 (46)
	5,000 and over	9	7 (78)

*Total number of patients in each category should be 90, since one patient on placebo and one patient on 6-MP had survival times equal to the median. Where total differs from 90, it is because platelet and/or blast data were unavailable for initial status.

†Median survival time from start of study for 6-MP patients = 60 weeks; median survival time from start of study for placebo patients = 46 weeks; median survival time from start of study for non-random patients = 16.5 weeks.

The study of a completely inactive compound (placebo) in a remission maintenance study did not affect significantly the patients' overall survival. Thus, this experimental design is consistent with use of the best available therapy for leukemia while permitting study of new agents early in the disease.

The response of patients to 6-MP therapy is independent of response to prior corticosteroids therapy. The frequency of remission induction and duration of remissions with 6-MP therapy, and survival were similar for patients who responded to prior steroid therapy and for those who failed to respond. These findings support the concept that chemotherapeutic agents can be adequately tested at any phase of the disease and that patients are not characterized as "responders" or "non-responders" on the basis of response to other chemotherapy.[9,13]

The initial white blood cell count and the duration of the interval between onset of symptoms and diagnosis have been shown to be related to survival.[11,13]

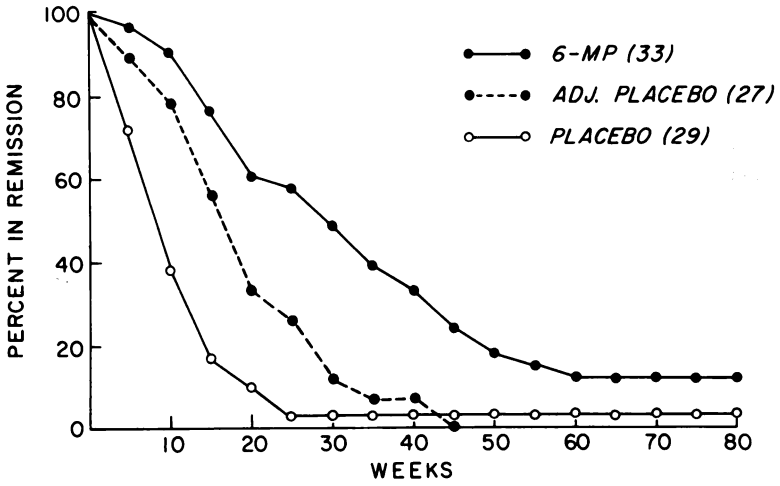

Fig. 7.—Duration of remissions for patients maintained on 6-MP and placebo compared to an adjusted placebo curve.

The higher the white cell count, or the shorter the period from symptoms to diagnosis, the poorer the prognosis. The present study defines the underlying reasons for this. Patients with high white cell counts or short intervals between symptoms and diagnosis had a lower probability of responding to steroid therapy for remission induction. Moreover, even if remission was induced the duration of their remissions was shorter, whether 6-MP or placebo maintenance therapy was used. Finally, such patients have a shorter survival than other patients showing the same response to therapy.

The observation that 6-MP may prolong remissions in patients in whom it would fail to induce remissions suggests that these two activities are not identical. Moreover, chemotherapeutic agents differ markedly in these two activities. Adrenal corticosteroids can induce complete remission in approximately 80 per cent of patients with ALL under 15 years of age, but has poor activity for remission maintenance. In contrast, 6-MP induces complete remission in only 27 per cent of such patients[7] but has good ability to maintain remissions. Perhaps there are agents that are almost inactive as regards remission induction which could prove useful for remission maintenance. Clinical study of these two separate parameters of antileukemic activity may provide data for more precise correlation with preclinical anti-tumor screening systems.

Summary

The effect of 6-MP therapy on the duration of remissions induced by adrenal corticosteroids has been studied as a model for testing of new agents. Ninety-two patients under age 20 entered the study and were accepted for analysis. Sixty-two (67 per cent) had complete or partial remissions induced by corticosteroids. Patients in remission were randomly assigned to maintenance therapy with either 6-MP or placebo. The median duration of 6-MP-maintained complete remissions was 33 weeks and for placebo, 9 weeks. A sequential experimental design was used to analyze remission times while the study was in

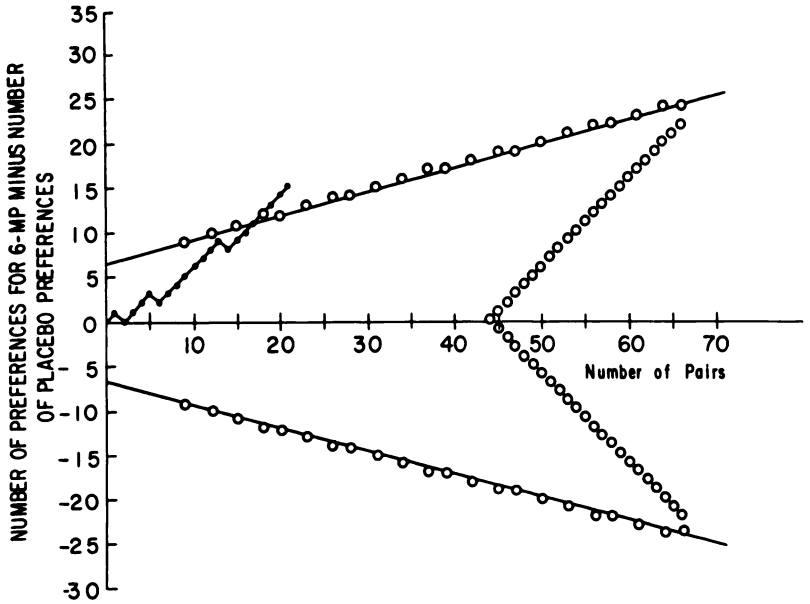

Fig. 8.—Chart for restricted sequential procedure applied to preferences designed to be sensitive to proportion of 6-MP or placebo preferences = 0.75.

progress. This resulted in the study being stopped after analysis of the remission times of 21 pairs of patients (42 patients). Overall survival was not significantly different for the two treatment programs, since patients maintained on placebo were treated with 6-MP when relapse occurred.

The activity of the known active antileukemic compound 6-MP was readily detected by this experimental design without compromise of optimal survival. Such a design should prove useful for the evaluation of new agents and also permit study of the remission maintenance activity of a compound separately from its remission inducing activity.

Summario in Interlingua

Le effecto de 6-mercaptopurina super le duration del remissiones inducite in acute leucemia per adreno-corticosteroides esseva studiate como modello pro le evalutation de altere nove agentes. Novanta-duo patientes de etates de minus que 20 annos esseva registrate pro le studio e poteva esser acceptate pro le analyse. Sexanta-duo (67 pro cento) habeva remissiones partial o complete, inducite per corticosteroides. Patientes in remission esseva gruppate aleatorimente pro therapia de mantenentia con (1) 6-mercaptopurina o (2) un placebo. Le duration median del complete remissiones mantenite per medio de 6-mercaptopurina esseva 33 septimanas. In le gruppo a placebo, iste duration esseva 9 septimanas. Un plano sequential de experimentation esseva usate pro analysar le tempores de remission durante que le studio esseva in progresso. Isto resultava in que le studio esseva suspendite post le analyse del tempores de remission in 21 pares de patientes (42 subjectos). Le superviventia general non esseva significativemente differente inter le duo pro-

Table 10.—*Preferences for 6-MP and Placebo in Sequential Phase of Study (Phase II)*

Pair	Remission Status	Drug	Length of Remission (wks.)	Preference
1	partial	placebo	1	6-MP
	partial	6-MP	10	
2	complete	placebo	22	placebo
	complete	6-MP	7	
3	complete	placebo	3	6-MP
	complete	6-MP	32+	
4	complete	placebo	12	6-MP
	complete	6-MP	23	
5	complete	placebo	8	6-MP
	complete	6-MP	22	
6	partial	placebo	17	placebo
	partial	6-MP	6	
7	complete	placebo	2	6-MP
	complete	6-MP	16	
8	complete	placebo	11	6-MP
	complete	6-MP	34+	
9	complete	placebo	8	6-MP
	complete	6-MP	32+	
10	complete	placebo	12	6-MP
	complete	6-MP	25+	
11	complete	placebo	2	6-MP
	complete	6-MP	11+	
12	partial	placebo	5	6-MP
	partial	6-MP	20+	
13	complete	placebo	4	6-MP
	complete	6-MP	19+	
14	complete	placebo	15	placebo
	complete	6-MP	6	
15	complete	placebo	8	6-MP
	complete	6-MP	17+	
16	partial	placebo	23	6-MP
	partial	6-MP	35+	
17	partial	placebo	5	6-MP
	partial	6-MP	6	
18	complete	placebo	11	6-MP
	complete	6-MP	13	
19	complete	placebo	4	6-MP
	complete	6-MP	9+	
20	complete	placebo	1	6-MP
	complete	6-MP	6+	
21	complete	placebo	8	6-MP
	complete	6-MP	10+	

grammas therapeutic, proque patientes mantenite con placebo recipeva 6-mercaptopurina quando un recidiva occurreva.

Le activitate del cognoscitemente active composito antileucemic 6-mercaptopurina esseva prestemente detegite in iste plano experimental sin compromitter le optime superviventia possibile. Un tal plano va provar se utile in le evalutation de nove agentes. Illo va etiam esser de valor in tanto que illo

permitte le studio del activitate de un composito in le mantenentia del remission separatemente ab su capacitate de inducer le remission.

APPENDIX

The comparison of the lengths of remission maintained on 6-MP and placebo was made using a restricted sequential procedure originally developed by Armitage.[14] The patients at each institution were paired according to remission status [complete (A-1) or partial (A-2)], one patient receiving 6-MP and the other placebo by a random allocation. As the patients relapsed from remission, a preference was recorded for 6-MP or placebo depending upon which therapy resulted in the longest remission. The purpose of the sequential design was to enable the trial to be stopped as soon as it could be established that one of the treatments was superior to the other. For further discussion of when sequential designs may be useful, see Armitage.[15]

The trial was designed to be sensitive to a proportion of preferences of 0.75 favoring either therapy, i.e., if the true proportion of preferences for 6-MP or placebo was 0.75, the probability of concluding that the proper therapy was in fact superior was 0.95. (This was roughly equivalent to trying to detect a 20-week difference in average remission times.) If there was really no difference between the therapies the probability was 0.95 that the trial would end showing no real difference. A chart designed to meet the above objectives is given in figure 8.

When a preference was available from a pair of patients, a point was plotted on the chart, one unit to the right and one unit up from the zero point for a 6-MP preference and one unit to the right and one unit down for a placebo preference. Thus, the difference between the number of 6-MP and placebo preferences could be read from the vertical axis after a given number of preferences had been recorded. If the sample path crosses the upper (or lower) boundary, a decision is made favoring 6-MP (or placebo). If the boundary to the right is crossed, then it is concluded that there is no real difference between treatments. The design provided a fixed upper limit to the number of patients entered in the trial. Thus, the maximum number of pairs of patients was 66 and the minimum number was nine.

The results from the pairs of patients entered in the trial are given in table 10 and plotted on figure 8. The lengths of remissions are those that were available at the time the decision was made to halt the trial in April 1960. The decision was made to stop the trial after 21 preferences were recorded. Actually, the trial could have been stopped after 18 preferences were recorded, but data on remission times were gathered only about every 3 months, just prior to a group meeting.

Note that 12 patients were still in remission at the time the study was stopped, though a preference could be recorded for each of the 21 pairs of patients. The entry of patients into the study was stopped while these 12 patients were still being studied. Of course, it is inherent in the design of such a trial that reliable data be submitted by each investigator. There is the danger that some of the patients will not be treated according to protocol and hence their data will be invalid. In this trial, the results from one pair of patients were later invalidated so it was fortunate that a number of extra pairs of patients was available.

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