CHEMOTHERAPY OF ACUTE MYELOID LEUKAEMIA IN ADULTS

MEDICAL RESEARCH COUNCIL

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Summary.—Two hundred and fifty patients with acute myeloid leukaemia (AML) were randomized between 2 regimens of chemotherapy: TRAP and BARTS III. Overall, patients randomized to TRAP, which was the more intensive of the 2 regimens, fared slightly better ($P=0.06$) than those on BARTS III. However, the improvement in survival associated with more intensive chemotherapy was substantial only for patients who had favourable prognostic features at presentation, such as a normal total leucocyte count, or absence of palpable liver, or, especially, age under 40. Indeed, for patients under 40, those allocated to the more intensive regimen (TRAP) lived considerably longer than those allocated to BARTS III ($P<0.002$) while for patients over 40 there was no material difference in survival between patients on the 2 protocols. It thus appears that intensive chemotherapy is likely to be more effective when favourable prognostic features are recorded.

IN THE Medical Research Council's 5th acute myeloid leukaemia (AML) trial, a 4-drug treatment schedule, RAMP (daunorubicin (Rubicidin), cytosine arabinoside, mercaptopurine, prednisone) used in the previous trial was compared with one or other of two 2-drug schedules in which cytosine arabinoside (AraC) was administered in combination with either thioguanine or daunorubicin (DR). The AraC/DR 2-drug combination, which seemed to be the best of these 3 treatments, was not statistically significantly better than the other 2 (MRC, 1974; 1975). However, this treatment is unlikely to be much worse than, and was not more toxic than, the other 2. Consequently, we decided to carry over this "best arm", or something very like it (*i.e.* "BARTS

III" chemotherapy, see below), from the 5th trial into the 6th trial, part of which we now report.

The Medical Research Council's "6th AML trial" in fact consists of 2 entirely separate trials. At some centres the "AML 6 immunotherapy" trial was organized to determine the value of adding immunotherapy to a standard form, (BARTS III) of chemotherapy closely resembling the best arm of the 5th trial (MRC, 1978; Harris *et al.*, 1978). At other centres the "AML 6 chemotherapy" trial was organized to determine whether more intensive chemotherapy would be more effective than BARTS III. In 1972 a pilot trial in the MRC Leukaemia Unit of a more intensive multiple-drug regimen (TRAP) had yielded promising results

(Spiers *et al.*, 1977). The MRC 6th AML chemotherapy trial which we now report, therefore compared, by random allocation of newly diagnosed AML patients, these 2 regimens, TRAP and BARTS III, to see whether the extra toxicity expected from TRAP would be compensated for by higher remission rates and better survival.

THE PROTOCOLS

BARTS III Chemotherapy

Remission-induction therapy.—Five-day courses of daunorubicin (DR) and cytosine arabinoside (Ara-C) with 5-day intervals between the last day of one course and the first day of the next.

Each 5-day course consisted of daily i.v. injections of Ara-C 70 mg/m² (2 mg/kg) plus, on the first day, DR 55 mg/m² (1.5 mg/kg) by fast injection just before the first injection of Ara-C. (In the MRC 5th trial schedule, the Ara-C was administered in 12-hourly doses, but the schedules were otherwise identical.)

Courses were to be continued until marrow aspirated on the day before the next course fell due showed hypoplasia with few or no residual blasts, after which 2 or 3 weeks without treatment were allowed. When marrow regeneration was recorded, and upward trends in the haemoglobin concentration and neutrophil and platelet counts were apparent, one further (consolidation) course was to be administered before proceeding to the maintenance schedule. If blast cells persisted in the marrow when the 5th course was due, the doses of DR and Ara-C were to be increased by 20%.

Maintenance chemotherapy.—Five-day courses of (i) Ara-C and thioguanine (TG), and of (ii) Ara-C with DR on Day 1 only, were alternated at monthly intervals until the onset of relapse. The doses of Ara-C and DR were the same as for induction therapy, and the daily dose of TG was 70 mg/m² (2 mg/kg) by mouth. Maintenance chemotherapy was started 1 month after the last consolidation course.

The TRAP Programme

The TRAP programme was designed in the MRC Leukaemia Unit by Dr A. S. D. Spiers. The remission-induction schedule was based on one of the schedules included in the 5th trial, but with thioguanine substituted for

mercaptopurine, and with courses repeated at 14-day intervals. The cyclical maintenance therapy was designed to expose the residual leukaemia cells to several different cytotoxic drugs, in the hope of reducing the rate of emergence of drug-resistant lines and thus deferring the onset of relapse.

TRAP remission-induction therapy.—Six 5-day courses of TRAP were administered in 12 weeks, with a 9-day interval between the last day of one course and the first day of the next.

Each course consisted of TG, 100 mg/m² daily for 5 days by mouth; DR, 40 mg/m² i.v. on the first day only; Ara-C, 100 mg/m² i.v. or i.m. daily for 3 days in the 1st course, 4 days in the 2nd course and 5 days thereafter; plus prednisolone, 30 mg/m² daily for 5 days by mouth. After the 3rd course, the doses of DR and Ara-C were to be increased by 20% on successive courses, if the blood-count trends permitted, to a maximum of 100 mg of DR and 300 mg of Ara-C.

TRAP cyclic maintenance therapy.—Each cycle of 20 weeks consisted of 2 courses of COAP (4 weeks), 3 of TRAP (6 weeks), 2 of POMP (4 weeks), and 3 of TRAP (6 weeks).

COAP was a 5-day course followed by a 9-day interval: cyclophosphamide, 100 mg/m² daily by mouth for 3 days in the first course, increasing, if possible, to 5 days; prednisolone, 100 mg b.d. for 5 days; vincristine 2 mg i.v. on the first day only; and Ara-C, 100 mg/m² i.v. or i.m. daily for 5 days.

POMP was a 5-day course followed by a 9-day interval: prednisolone, 100 mg b.d. for 5 days; vincristine, 2 mg i.v. on the first day only; methotrexate, 7.5 mg/m² i.v. or i.m. daily for 3 days; and, for the first of each pair of courses, mercaptopurine, 300 mg/m² for 3 days. Each course could be delayed for 1 week if the blood counts were considered suboptimal.

Eligibility for entry to the trial

All AML patients, irrespective of age, were eligible for entry to the trial, provided they had not received any prior treatment with cytotoxic drugs. Patients suffering from undifferentiated blast-cell leukaemia were entered into this trial if aged over 25, excluded from it if aged under 20, and admitted or not at the clinician's discretion if aged between 20 and 25. Patients with leukaemia supervening on pre-existing haematological

disorders were not eligible for entry to the present study, nor were patients presenting at the 4 centres which were undertaking the MRC immunotherapy trial (MRC, 1978; Harris *et al.*, 1978). Patients who were entered were immediately randomized, in equal proportions, between TRAP and BARTS III.

STATISTICAL METHODS

These are as described in the report on statistical methods to the Medical Research Council's Leukaemia Steering Committee (Peto *et al.*, 1976; 1977). They chiefly involve the plotting of Kaplan-Meier life-table estimates of the percentages alive at various times up to $2\frac{1}{2}$ years after entry, after achieving remission, or after relapse, to illustrate various patterns of survival, and the calculation of logrank *P*-values to test the statistical significance of any apparent differences in survival or remission duration. For the latter, exact variance calculations were performed (*ibid.*, Statistical Note 7) and continuity corrections were not used (*ibid.*, p. 38). (Because follow-up is complete to 3 years after entry, and to $2\frac{1}{2}$ years after remission induction for all long survivors, these life-table plots of survival from entry or from remission reduce to simple graphs of the observed percentages alive at various times.)

PATIENTS ENTERED

Between January 1973 and November 1974, 250 patients newly diagnosed as suffering from AML were admitted to the trial. 125 were allocated randomly to receive BARTS III chemotherapy, and 125 to the TRAP programme of treatment. Intake was ended when an interim analysis of the duration of survival did not, in the autumn of 1974, indicate any substantial difference between the 2 treatments, for some participants feared that side

effects and complications associated with the TRAP programme would be unacceptable, unless the results of treatment were considerably better than those obtained with the BARTS III schedule. (Prolonged follow-up has shown, however, that there is some survival advantage in using TRAP, and that its toxicity is not severe.)

DATA COLLECTED

At presentation most of the following information was recorded for each of 244 of the 250 patients: platelet and haemoglobin levels; leucocyte (WBC), blast-cell, neutrophil and monocyte counts; whether or not there were gum deposits, skin deposits and haemorrhagic manifestations; and whether or not the liver, spleen and nodes were palpable.

Patients were followed up until 1 January 1978, and the dates of any remissions, relapses or deaths were recorded* and the causes of death were sought. Each patient has thus been followed to death or for at least 3 years.

RESULTS

The statistical analysis of the results is presented in 9 tables in the Appendix (AT I to AT IX) and in 5 figures showing the duration of survival in different subgroups of patients.

Relation between treatment and survival (AT I)

Patients randomized to TRAP did slightly better than those on BARTS III (Fig. 1). Remission was achieved by 82 patients (32% of those randomized), 42 of whom were on TRAP and 40 on BARTS III. Whilst the remission rate was similar for both treatments, there was a small, but almost statistically significant ($P=0.06$), difference between their survival

* The date of death was not known for one patient who had refused treatment and was believed to have died. Her date of death was taken to be 60 days after randomization. The date of remission was not known for one patient who was still alive one year after randomization, and it was assumed that she achieved remission after 60 days.

curves. Patients randomized to TRAP had a 30% probability of surviving for one year compared with 23% for those on BARTS III. Whilst the duration of first remissions was similar for both treatments,

the duration of survival after relapse was statistically significantly better for TRAP than for BARTS III ($\chi^2 = 6.1$, $DF = 1$, $0.02 > P > 0.01$). This produced a slightly better prognosis after remission for

FIG. 1.—(a) Duration of survival for 125 patients randomized to BARTS III and 125 randomized to TRAP.
 (b) Duration of survival after first remission for the 40 patients on BARTS III and the 42 on TRAP who achieved remission.
 (c) (opposite) Estimated duration of survival after first relapse for the 31 patients on BARTS III and the 31 on TRAP who relapsed in their first remission.

FIG. 1(c)

FIG. 2.—Duration of survival for the 74 patients aged <40, the 92 aged 40–59 and the 84 aged ≥60.

patients on TRAP ($P = 0.13$) who had a 43% probability of surviving 2 years after remission, compared with 20% for those on BARTS III.

The improvement effected by using a more intensive programme (TRAP) rather than a gentle one (BARTS III) was more marked in the patients with more favour-

able prognostic features. This was so whether the patients were sub-divided into "favourable" or "unfavourable" prognosis groups on the basis of age, WBC, blast-cell count, haemoglobin level or on whether the liver was palpable at presentation. In each case the more intensive (TRAP) schedule appeared to be no better

FIG. 3.—(a) Duration of survival for the 39 patients on BARTS III and the 35 on TRAP, who were aged <40 .
 (b) Duration of survival for the 86 patients on BARTS III and the 90 on TRAP who were aged ≥ 40 .
 (c) (opposite) Duration of survival after first remission for the 15 patients on BARTS III and the 20 on TRAP, who were aged <40 and achieved remission.
 (d) Duration of survival after first remission for the 25 patients on BARTS III and the 22 on TRAP, who were aged ≥ 40 and achieved remission.

FIG. 3(c)

FIG. 3(d)

than the gentler (BARTS III) programme for *bad* prognosis patients, but among patients whose prognosis was better than average the more intensive antileukaemic treatment appeared to be somewhat more effective. Appendix Tables (AT) II-VII show this in detail.

Relation between age at presentation and survival (AT II)

The age of patients ranged from 2 years old to 77, with 74 patients (30%) under 40. The proportion who achieved remission declined considerably with increasing age and the survival curves showed a strong

FIG. 4.—Duration of survival for the 28 patients with WBC $5-9 \times 10^9/l$, the 81 with WBC $10-49 \times 10^9/l$ and the 62 with WBC $\geq 50 \times 10^9/l$. The 73 with WBC $< 5 \times 10^9/l$ (not shown) had similar survival to those with 10–49.

trend with age ($P < 0.0001$, Fig. 2). However, there was no significant trend with age in survival from the onset of remission, though 40% (6/15) of patients aged 60 or more relapsed within 6 months of remission, compared with 16% (11/67) of the younger patients.

Among patients under 40 years old, those on TRAP had the higher remission rate (57% as against 38% on BARTS III), and, moreover, patients aged under 40 who achieved remission also survived longer thereafter if they were on TRAP than if they were on BARTS III ($P = 0.04$). Overall survival, which includes the survival before remission is achieved, the duration of remission, and the length of survival after relapse was, therefore, highly significantly better on TRAP than on BARTS III for patients under 40 ($P = 0.002$). However, among patients of 40 and older there was no material difference between the 2 treatments in remission rate or in survival following remission and so in overall survival (Fig. 3) although survival after relapse appeared to be better on TRAP.

Relation between WBC at presentation and survival (AT III)

This is shown in Fig. 4. (Patients with WBC $< 5 \times 10^9/l$ had similar survival to those with $10-49 \times 10^9/l$ and are not represented in the figure.) There was a significant ($P = 0.02$) tendency for those with higher WBC to fare worse, and 38% of patients whose WBC was less than $10 \times 10^9/l$ achieved remission compared with 30% for those with $10 \times 10^9/l$ or more. There was a small but not statistically significant effect of original WBC on the prognosis after remission. Thus, although the WBC is statistically significantly associated with survival, the strength of the association is much less than in the case of acute lymphoblastic leukaemia, where the presenting WBC is of critical importance both for overall survival and for length of first remission.

Among patients with WBC $< 10 \times 10^9/l$, those randomized to TRAP had a 40% remission rate compared with 35% for BARTS III, and a better prognosis after remission than those on BARTS III, though this was not statistically signi-

ficant ($P=0.16$). Hence, among these low-WBC patients, overall survival was better for those treated with TRAP ($P=0.06$). There were, however, no material differences between the treatments among patients with a WBC of $10 \times 10^9/l$ or more.

The combined effects of age and WBC on survival (AT IV)

For the 29 patients with WBC less than $10 \times 10^9/l$ and who were also under 40, those on TRAP fared highly significantly better than those on BARTS III ($P=0.007$), although since we are describing the single selected subgroup which best illustrates our point, this nominal P -value is exaggerated. Among those with WBC of $10 \times 10^9/l$ or more and who were also under 40, there was also some deficit of deaths for those on TRAP though this was not statistically significant. Among patients aged over 40 there was no difference between treatments, whether the WBC was high or low. This suggests that age alone (over or under 40) may be a sufficient determinant of whether intensive or moderate chemotherapy is preferable, but that perhaps for patients aged

around 40 or so a WBC below $10 \times 10^9/l$ indicates more intensive treatment.

Relation of blast-cell count at presentation and survival (AT V)

Patients with $<5 \times 10^9/l$ of blast cells had a remission rate of 39%, compared with 27% for those with $5 \times 10^9/l$ or more, and there was a statistically significant downward trend ($P=0.005$) in the survival curves with increasing blast-cell counts. This trend was not reduced when allowance was made for age. There was a small but not statistically significant effect on prognosis after remission.

It has been shown that patients with blast cells $\geq 100 \times 10^9/l$ have a poor prognosis (Harris, 1978) and this was confirmed in the present study. The 21 such patients in this group had significantly worse prognosis ($P=0.003$), with only 11 surviving the first month and 3 surviving more than one year.

Among patients whose blast-cell counts were $<5 \times 10^9/l$, prognosis was somewhat better with TRAP, while among patients with blast-cell counts $\geq 5 \times 10^9/l$ the difference between the treatments was smaller.

FIG. 5.—Duration of survival for the 78 patients for whom the liver was recorded as palpable and the 166 for whom the liver was recorded as not palpable at presentation.

Relation between haemoglobin level at presentation and survival (AT VI)

The 59 patients with haemoglobin levels of 10 g/100 ml or more had a 41% remission rate compared with 31% for those whose Hb was less than 10, and there was a significant trend between the survival curves, $P=0.02$. Among patients with Hb levels ≥ 10 g/100 ml, 48% on TRAP achieved remission compared with 33% on BARTS III. For those with lower levels the rates were 29% and 33% respectively. Within any one particular Hb category (<7.5 , $7.5-9.9$, $10+$) the difference between TRAP and BARTS III was not statistically significant, perhaps because of small numbers, but an analysis of the effects of treatment retrospectively stratified for Hb (by summation of the observed and expected numbers in the lower part of AT VI) yields P -values like those in Table I.

Relation between state of the liver at presentation and survival (AT VII)

Physicians were asked to report whether the liver was palpable at presentation. Although this is an unreliable assessment, patients reported to have had a palpable liver (almost one-third of the total) had a considerably worse prognosis than the others ($P=0.0003$, Fig. 5). Their 6-month survival rate was 35% compared with 48% among patients with no record of liver enlargement, and the one-year rates were 15% and 32% respectively. These patients had a remission rate of only 26% and there was also a statistically significant ($P=0.005$) difference in survival after remission. Among patients entering remission, only 20% of those originally noted with a palpably enlarged liver survived for 2 or more years, while 39% of those whose liver was not palpable did so. The relevance of (recorded) liver enlargement was highly statistically significant in the patients over 40 ($P=0.003$) and was also present, though less markedly, in the younger group. This suggests that the presence of a palpable liver is an indepen-

dent prognostic feature. Among patients who were reported not to have an enlarged liver at presentation, those on TRAP had a 39% one-year survival rate compared with 24% for those on BARTS III; the difference between the survival curves was statistically significant ($P=0.01$). This treatment difference was even greater among those who were also under 40 ($\chi^2 = 16.5$, $DF = 1$, $P < 0.0001$). In contrast, among patients who were reported as having an enlarged liver, those randomized to BARTS III actually fared slightly better than those on TRAP, though this difference was not statistically significant ($P = 0.13$).

Relation between other features recorded at presentation and survival (AT VIII)

Several other presentation features were related to prognosis, but the effects were very small. Patients with platelet counts $\geq 50 \times 10^9/l$ had a slightly higher chance of remission, and tended to survive a little longer. Similarly, the presence of an enlarged spleen, gum or skin deposits, or haemorrhagic manifestation at presentation were associated with a lower remission rate.

Effects of retrospective stratification on treatment (AT IX)

Finally, to check that the treatment comparison was not biased by any chance allocation of too many good-prognosis patients to one treatment arm, the treatment χ^2 was computed after retrospective stratification for various indices of prognosis. As may be seen, stratification did not result in any striking changes in the treatment effect, which remained at $P \approx 0.1$ in all patients together. It is only in the good prognosis subgroups (see above) that any marked superiority of TRAP is apparent.

DISCUSSION

The duration of survival in AML depends largely on whether or not the patient enters remission, arbitrarily de-

defined as a blast-cell count in the marrow below 5% when regeneration has occurred after remission-induction therapy. This definition provides only a crude index of the number of leukaemia cells surviving remission-induction therapy, and cannot distinguish cases in which the number of surviving cells is small from those in which it is much larger but still within the 5% limit of the definition. If the rate of proliferation of surviving leukaemia cells were constant whatever their total number, the time to detectable relapse, and therefore the duration of remission, would be longest when the number of surviving cells was least. If the proportion of leukaemia cells destroyed is related to the intensity of therapy, more intensive therapy should leave fewer surviving cells, and should increase both the percentage of remissions induced and the duration of remission. The rate of proliferation of the surviving leukaemia cells might also be lowered by increasing the intensity of maintenance therapy, while the risk of emergence of drug-resistant cells might be reduced by regularly changing the drug combinations administered for maintenance therapy. The TRAP programme was designed with these aims, and the results of the uncontrolled pilot trial (Spiers *et al.*, 1977) suggested that the duration of remission had been considerably prolonged over those in published reports, the median duration being 66 weeks (range 28–208 weeks). It was not clear whether the increased percentage of remissions (60% of 25 patients) would be repeatable in a larger series.

The present trial was designed to compare the more intensive TRAP programme with the less intensive BARTS III protocol in a multi-centre trial. By random allocation 125 patients were treated according to the TRAP programme and 125 according to the BARTS III protocol. It is true that the overall results showed no significant difference between the two protocols in remission rate (32% for BARTS III and 34% for TRAP) or in duration of survival (23% of BARTS III patients and 30% of TRAP alive at one

year) but there was an indication that for the patients who entered remission, survival was superior in the TRAP group (43% alive 2 years after the onset of remission compared with 30% in the BARTS III group). Patients with a blast-cell count $\geq 100 \times 10^9/l$ at presentation have a very poor prognosis (Harris, 1978) as do those with hypergranular promyelocytic leukaemia (MRC, 1975). When the 32 patients in the present study with either of these features were removed from the analysis, the duration of survival for TRAP became significantly better than for BARTS III ($P=0.05$).

When the patients were divided into groups with and without favourable prognostic features, TRAP proved to be significantly better among the former in respect of remission rate, overall survival and survival after the onset of remission, the last reflecting more the longer survival after relapse than the longer duration of remission.

If it is indeed true that the relative merits of trial treatments are materially different, or even opposite, for different categories of patient, then quite large trials will be needed in order to clarify this reliably. Even in the present trials with 250 patients, there remains some doubt about the extent to which artefacts of chance have influenced the age-specific differences between TRAP and BARTS III, and in a trial with only 100 patients these patterns might have gone unnoticed.

The most important prognostic feature, as in previous trials (MRC, 1974; 1975) was age (Fig. 2), the overall survival decreasing in progressively older age groups. For the 74 patients under 40, the results were markedly superior in the TRAP group, for which, as compared with the BARTS III group, there was 57% and 38% of remissions, with 51% and 28% of all patients surviving 2 years from the onset of remission. Similar trends are seen when the results are analysed according to other independent features of prognostic significance, including leucocyte count at presentation (Table III), blast-

cell count at presentation (Table V), Hb concentration at presentation (Table VI) and the presence or absence of palpable liver enlargement at presentation (Table VII). In each case the advantage of treatment by the TRAP programme is chiefly apparent in the groups with more favourable prognostic features, namely leucocyte count $<10 \times 10^9/l$, blast-cell count $<5 \times 10^9/l$, Hb concentration ≥ 10 g/dl, or liver not palpable.

For patients with more than one favourable prognostic feature at presentation, *e.g.* age <40 and leucocyte count $<10 \times 10^9/l$, the apparent advantage of TRAP was especially marked (Table IV), but the numbers are small.

In contrast, for patients with unfavourable prognostic features, the TRAP programme gave no advantage over the gentler BARTS III protocol (Tables II–VII, Fig. 3b). The percentage of remissions was low in both treatment groups because of high fatality during remission-induction therapy. This reflects the inability of poor-risk patients to withstand the hazards of prolonged marrow failure. Potentially more effective therapy has no advantage in these patients unless they can be kept alive long enough to reap the benefits. It is not immediately apparent why the poor-risk TRAP patients who did enter remission failed to show the same prolongation of survival as the good-risk patients. A possible explanation was that they tolerated the intensive maintenance therapy poorly and so received inadequate treatment. However, inspection of the charts in the 2 groups does not show a marked difference in the amount of treatment received.

The present trial is the first in the series of MRC trials of multi-drug therapy for AML in which survival *after* complete remission had been induced differed between treatments. In the groups of good-risk patients concerned, the more intensive treatment programme led to higher remission rates and to longer survival after relapse in those patients who entered remission. For these patients, at least, the

inference must be that the future of chemotherapy lies in more intensive treatment rather than the gentler treatment advocated by Burge *et al.* (1975). The superior results of more intensive therapy, administered with adequate supportive care, have been shown in other trials and form the basis of the current trial. Thus, Stavem *et al.* (1977) using the TRAP programme, reported 7/56 patients surviving in complete remission for 4–6 years, having been off therapy for 1–3 years. Even more intensive remission-induction schedules have been reported to give remission rates $\sim 80\%$ (Gale & Cline, 1977; Rees *et al.*, 1977) and the remissions reported in elderly patients no doubt reflect the high quality of supportive care. For the poor-risk groups, it seems likely that improvement in supportive care during remission-induction therapy would reduce the risk of early death, and so increase the chance of entering remission. If this is true, more intensive therapy might improve the results of treatment in the same way as it has in the good-risk groups, but while supportive care is inadequate, more intensive therapy offers no advantage, and its use is difficult to justify because of the extra toxicity, extra cost and the high incidence of side effects.

The results of the present trial are not quite as good for either TRAP or BARTS III as in the original reports (Spiers *et al.*, 1977; Crowther *et al.*, 1970). It is often believed that multi-centre trials are inherently incapable of reproducing results reported by those who carried out the original trials, and that the standards of practice at the participating centres are somehow inferior to those at the originating centre. There is, however, a more likely explanation. The results of a new form of treatment administered to a group of patients arise both from the intrinsic merits of the treatment and from chance factors which may operate to give rise to results better or worse than the average for that treatment. Even if the treatment is, in fact, no more effective than conventional treatment, superior results in the

first series of patients treated will lead to early publication, whereas indifferent or inferior results will lead to the new method being abandoned. A new treatment that is, in fact, somewhat more effective than conventional treatment is certain to be reported with enthusiasm if the early results are, by chance, strikingly superior. Later trials involving larger numbers of patients will confirm the superiority of the treatment, but the results are likely to be less striking than those originally reported, as has been the case in the present trial. It will be recalled that the original figure of 62% of remissions for the BARTS III protocol dropped to 42% in a subsequent report by the same workers (Crowther *et al.*, 1973).

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Notes added in proof

(1) By 1 December 1978 a further 2 patients had died. In a subsequent statistical analysis the χ^2 for treatment became 2.99 for the total group, 9.84 for those aged under 40 and 0.03 for those aged 40 or more.

(2) It is of interest to compare the autumn 1978 results from the South West Oncology Group's adult acute leukaemia studies (personal communication from Dr K. B. McCredie) with the MRC results in our 6th AML chemotherapy and immunotherapy trials. Neither the British nor the American studies have all cases of AML referred to them, and this "selection" of patients might well exclude different proportions of those likely to die most

rapidly from the two studies (for example, a larger proportion of the British patients were old). Nevertheless, the American study is very large and it is noteworthy that in every age-group there was a larger proportion of remissions than in the present trial. Overall, 54% of their 465 AML patients remitted, which is comparable with the 52% of 148 patients in the MRC's AML6 immunotherapy trial (MRC, 1978) and considerably better than the 32% of 250 in the present trial. However, once remission was achieved, in the SWOG studies the subsequent disease-free survival was almost identical to that in both the MRC AML6 trials. In particular, a randomized comparison twice as large as the MRC immunotherapy comparison

showed no material difference between OAP chemotherapy and OAP + BCG chemoimmunotherapy. This is compatible with the view (which underlay the recent changes from the MRC 7th to the current 8th trial) that the overriding need is to put the most intensive efforts possible into AML remission induction.

APPENDIX

TABLES I to VIII present the relative death rates and percentages of remissions according to treatment, and to various features recorded at presentation. In the tables, we cite the uncorrected χ^2 statistic comparing the O's with the E's; DF denotes the degrees of freedom of this χ^2 , P denotes the P-value associated with such a χ^2 and, where relevant, NS indicates a non-significant (i.e. $P > 0.1$)

Survival among all patients					Survival from date of remission									
Group	No. of patients	No. of deaths (O)	Extent of exposure to risk		χ^2	No. of remissions (%)	Observed no. of deaths (O)	Extent of exposure to risk of death (E)	% alive after remission 12 mths 24 mths					
			O/E	6 mths 12 mths										
TABLE I: TREATMENT														
BARTS III	125	120	106.0	1.13	38	23	3.41 DF=1 P=0.06	40 (32)	35	28.9	1.21	65	28	2.30 NS
TRAP	125	115	129.0	0.89	49	30		42 (34)	32	38.1	0.84	74	43	
TABLE II: AGE AT PRESENTATION														
<i>Treatment in those aged <40</i>														
BARTS III	39	39	26.6	1.46	51	28	9.84 DF=1 P<0.002	15 (38)	15	9.8	1.53	60	27	4.40 DF=1 P=0.04
TRAP	35	29	41.4	0.70	77	51		20 (57)	14	19.2	0.73	75	50	
<i>Treatment in those aged ≥40</i>														
BARTS III	86	81	79.4	1.02	33	21	0.06 NS	25 (29)	20	19.2	1.04	68	28	0.06 NS
TRAP	90	86	87.6	0.98	38	21		22 (24)	18	18.8	0.96	73	36	
TABLE III: WBC ($\times 10^9/l$) AT PRESENTATION														
<i>Treatment in those with WBC <10 × 10⁹/l</i>														
BARTS III	46	43	34.3	1.25	39	20	3.59 DF=1 P=0.06	16 (35)	13	9.5	1.37	50	31	1.99 NS
TRAP	55	48	56.7	0.85	56	40		22 (40)	15	18.5	0.81	82	50	
<i>Treatment in those with WBC ≥10 × 10⁹/l</i>														
BARTS III	74	72	68.4	1.05	38	26	0.37 NS	23 (31)	21	18.9	1.11	74	22	0.46 NS
TRAP	69	66	69.6	0.95	44	22		20 (29)	17	19.1	0.89	65	35	

Survival among all patients						Survival from date of remission							
Group	No. of patients	Observed no. of deaths (O)	Extent of exposure to risk of death (E)	O/E	χ^2	No. of remissions (%)	Observed no. of deaths (O)	Extent of exposure to risk of death (E)	% alive after remission				
									6 mths	12 mths	12 mths	24 mths	
TABLE IV: WBC AND AGE AT PRESENTATION													
<i>Treatment in those with WBC < 10 × 10⁹/l and age < 40</i>													
BARTS III	12	12	6.4	1.88	58	25	7.20 DF=1 P=0.007	6 (50)	2.7	2.20	33	17	5.29 DF=1 P=0.02
TRAP	17	12	17.6	0.68	88	65		12 (71)	10.3	0.68	75	58	
<i>Treatment in those with WBC ≥ 10 × 10⁹/l and age < 40</i>													
BARTS III	25	25	21.4	1.17	48	32	1.24 NS	9 (36)	8.3	1.09	78	33	0.14 NS
TRAP	18	17	20.6	0.83	67	39		8 (44)	7.7	0.90	75	38	
<i>Treatment in those with WBC < 10 × 10⁹/l and age ≥ 40</i>													
BARTS III	34	31	29.7	1.04	32	18	0.11 NS	10 (29)	7	0.97	60	40	0.01 NS
TRAP	38	36	37.3	0.96	42	29		10 (26)	8	1.03	90	40	
<i>Treatment in those with WBC ≥ 10 × 10⁹/l and age ≥ 40</i>													
BARTS III	49	47	47.0	1.00	33	22	0.00 NS	14 (29)	12	1.06	71	14	0.09 NS
TRAP	51	49	49.0	1.00	35	16		12 (24)	10	0.93	58	33	

TABLE V: BLAST-CELL COUNT (× 10⁹/l) AT PRESENTATION

<1	75	68	76.3	0.89	47	28	26 (35)	38	41.6	0.89	68	38	
4-9	53	48	61.0	0.79	57	36	24 (45)						
2-49	47	44	41.7	1.05	40	26	13 (28)	28	23.4	1.20	71	29	1.44 NS
≥25	69	69	49.9	1.38	33	19	18 (26)						
<i>Treatment in those with < 5 × 10⁹/l blasts</i>													
BARTS III	63	59	50.2	1.18	44	24	24 (38)	20	15.5	1.29	58	29	
TRAP	65	57	65.8	0.87	57	38	26 (40)	18	22.5	0.80	77	46	2.20 NS
<i>Treatment in those with ≥ 5 × 10⁹/l blasts</i>													
BARTS III	57	56	50.8	1.10	32	23	15 (26)	14	12.3	1.14	73	20	0.46 NS
TRAP	59	57	62.2	0.92	41	20	16 (27)	14	15.7	0.89	69	38	

TABLE VI: HAEMOGLOBIN CONCENTRATION (g/dl) AT PRESENTATION

<7.5	85	83	71.2	1.17	42	21	5.31	26 (31)	24	16.8	1.43	58	23	3.70
7.5-9.9	99	92	88.3	1.04	40	26	DF=1	31 (31)	24	25.9	0.93	74	32	DF=1
≥10.0	59	53	68.6	0.77	52	36	P=0.02	24 (41)	18	23.3	0.77	75	50	P=0.05
<i>Treatment in those with Hb <7.5 g/dl</i>														
BARTS III	42	41	37.3	1.10	40	12	0.70	14 (33)	13	9.5	1.37	50	7	2.31
TRAP	43	42	45.7	0.92	44	23	NS	12 (28)	11	14.5	0.76	67	42	NS
<i>Treatment in those with Hb 7.5-9.9 g/dl</i>														
BARTS III	47	45	39.5	1.14	36	26	1.34	15 (32)	13	10.1	1.29	67	27	1.47
TRAP	52	47	52.5	0.90	44	27	NS	16 (31)	11	13.9	0.79	81	38	NS
<i>Treatment in those with Hb ≥10.0 g/dl</i>														
BARTS III	30	28	23.0	1.22	40	27	1.95	10 (33)	8	7.5	1.07	80	50	0.06
TRAP	29	25	30.0	0.83	66	45	NS	14 (48)	10	10.5	0.95	71	50	NS

TABLE VII: STATE OF THE LIVER AT PRESENTATION

Not palpable	166	151	174.1	0.87	48	32	13.1	61 (37)	46	54.5	0.84	74	39	7.91
Palpable	78	78	54.9	1.42	35	15	DF=1	20 (26)	20	11.5	1.74	55	20	DF=1
<i>Treatment in those whose liver was not palpable</i>														
BARTS III	79	74	59.4	1.25	38	24	6.01	26 (33)	21	15.8	1.33	62	27	2.62
TRAP	87	77	91.6	0.84	58	39	DF=1	33 (40)	25	30.2	0.83	83	49	NS
<i>Treatment in those whose liver was palpable</i>														
BARTS III	41	41	47.3	0.87	39	22	2.31	13 (32)	13	15.8	0.82	69	23	2.53
TRAP	37	37	30.7	1.21	30	8	NS	7 (19)	7	4.2	1.66	29	14	NS

TABLE VIII: OTHER FACTORS AT PRESENTATION

<i>Platelet level ($\times 10^9/l$)</i>														
<25	68	66	52.3	1.26	35	22		18 (26)	16	15.1	1.06	—	—	—
25-49	59	57	50.7	1.12	37	22	5.36	18 (31)	16	9.9	1.62	—	—	0.15
50-249	69	61	77.1	0.79	49	33	DF=1	24 (35)	16	27.1	0.59	—	—	NS
≥100	47	44	47.8	0.92	55	30	P=0.02	21 (45)	18	13.9	1.30	—	—	—
<i>State of spleen</i>														
Not palpable	165	155	158.5	0.98	46	28		59 (36)	49	45.2	1.08	—	—	—
Palpable	79	74	70.5	1.05	40	23	0.25	22 (28)	17	20.8	0.82	—	—	1.00
<i>Gum or skin deposits</i>														
Absent	205	192	199.2	0.96	45	29	2.01	72 (35)	59	60.3	0.98	—	—	0.35
Present	39	37	29.8	1.24	38	13	NS	9 (23)	7	5.7	1.24	—	—	NS
<i>Haemorrhagic manifestations</i>														
Absent	114	105	117.2	0.90	48	30	2.64	44 (39)	35	36.9	0.95	—	—	0.22
Present	130	124	111.8	1.11	40	24	NS	37 (28)	31	29.1	1.06	—	—	NS

TABLE IX.—*Effects of retrospective stratification for various presentation features on the difference in overall survival associated with treatment*

Features for which treatment comparison is adjusted	BARTS III		TRAP		χ^2
	Observed no. of deaths (O)	Extent of exposure to risk of death* (E)	O	E*	
None	120	106.0	115	129.0	3.41
Age	120	105.2	115	129.8	3.92
WBC	115	103.7	114	125.3	2.36
WBC and Age	115	104.5	114	124.5	2.03
Blasts	115	101.8	114	127.2	3.19
Hb	114	99.8	114	128.2	3.66
Liver palpability	115	106.7	114	122.3	1.31
Centre	120	108.2	115	126.8	2.51

* Retrospectively stratified for one feature (see Peto *et al.*, (1977) section 22). The observed numbers vary slightly because patients for whom a particular feature was inadvertently not recorded at presentation are excluded from the corresponding adjusted analysis of survival.