Chemotherapeutic Options in Chronic Lymphocytic Leukemia: a Meta-analysis of the Randomized Trials

CLL Trialists' Collaborative Group

Background: **The randomized trials that evaluate the timing and intensity of initial chemotherapy for chronic lymphocytic leukemia (CLL) have, in general, been too small to provide separately reliable results. We compared the effects on survival of the following: *a*) immediate versus deferred chemotherapy for early-stage CLL and *b*) combination chemotherapy (e.g., cyclophosphamide and vincristine plus prednisone/prednisolone [COP] or COP plus doxorubicin [CHOP]) versus single-agent chlorambucil as first-line treatment for more advanced disease.** ***Methods:*** **All relevant randomized trials, whether published or not, were sought for a collaborative meta-analysis involving centralized review of the data for each patient.** ***Results:*** **There were 2048 patients with early disease in six trials of immediate versus deferred chemotherapy (chlorambucil or chlorambucil plus prednisone/prednisolone). The 10-year survival was slightly worse (but not statistically significantly so) with immediate chemotherapy (44% versus 47% survival; difference = −3%; 95% confidence interval [CI] = −10% to 4%). There were another 2022 patients in 10 trials of combination chemotherapy versus chlorambucil, with or without prednisone/prednisolone. The 5-year survival was 48% in both cases (difference = 0%; 95% CI = −6% to 5%). A subgroup of six of these 10 trials involved an anthracycline-containing regimen but again overall survival appeared no better than with chlorambucil (anthracycline-based regimen: 325 deaths among 627 patients; chlorambucil: 306 deaths among 636 patients; death rate ratio = 1.07; 95% CI = 0.91–1.25; not statistically significant).** ***Conclusions:*** **In terms of survival, these trials support a conservative treatment strategy for CLL, i.e., no chemotherapy for most patients with early-stage disease, and single-agent chlorambucil as the first line of treatment for most patients with advanced disease, with no evidence of benefit from early inclusion of an anthracycline. This strategy will, however, need to be reconsidered as mature results become available from trials of other agents. [J Natl Cancer Inst 1999;91:861–8]**

Chronic lymphocytic leukemia (CLL) is chiefly a disease of middle and old age. An increasing proportion of patients are diagnosed at an early stage of the disease, often with few or no symptoms, and may survive for several years with little progression of their disease, eventually dying from unrelated causes *(1–4).*

Chlorambucil, with or without steroids (prednisone or prednisolone), has been widely used as the first line of treatment for CLL and often provides a period of relief from any symptoms, even in advanced disease. However, for patients with early-stage disease and no serious symptoms, there has been much uncertainty as to whether such chemotherapy should be started immediately or whether it should usually be deferred for some months or years. Several randomized trials have therefore compared the policy of starting chlorambucil immediately with that of deferring treatment until required for the relief of symptoms. A meta-analysis of their survival results is presented, based on collaborative review of the detailed data from each study.

Advanced CLL generally requires immediate cytotoxic treatment, and several randomized trials have compared combination chemotherapy versus single-agent chlorambucil. All, however, have been too small to provide a reliable answer on their own, so again a meta-analysis is presented. The combination chemotherapy regimen was cyclophosphamide, vincristine (Oncovin) plus prednisone/prednisolone (COP) in some trials and COP plus doxorubicin (14-hydroxydaunomycin) (CHOP) in most others, only the second of which includes an anthracycline (*see* Table 1 for treatment schedules). The only other trial of combination chemotherapy versus chlorambucil was the recent, currently unpublished, Medical Research Council (MRC) CLL3 trial of adding epirubicin to chlorambucil. In addition to the trials of combination versus single-agent cytotoxic therapy, one small trial compared COP versus CHOP directly and reported a statistically significant advantage for the latter *(5).* This claim needs to be interpreted, however, in the light of the present meta-analyses of the trials of COP versus chlorambucil or of CHOP versus chlorambucil, since these involve much larger numbers and are therefore less subject to random error.

METHODS

The CLL Trialists' Collaborative Group was formed to bring together the results of all properly randomized CLL trials that began before the end of 1990.

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See "Notes" following "References" for names of collaborators.

Table 1. Relevant randomized chronic lymphocytic leukemia (CLL) trials that began before the end of 1990

Trial* (reference No.)	Entry period	Median follow-up, y	Eligible† stages	Drugs, doses (mg), and timings‡
Immediate versus deferred chemotherapy				
CALGB *(11)*	1976–1983	—	I or II	[Ch0.5/kg d1]/4w, escalated
MRC-CLL1 *(18)*	1978–1984	12	I or II	[Ch1.5/kg d1–3]/4w
MRC-CLL2 *(18)*	1984–1989	9	A	[Ch20/m^2 d1–3]/4w
FRE-CLL-80 *(13)*	1980–1985	11	A	[Ch0.1/kg] daily
FRE-CLL-85 *(14)*	1985–1990	6	A	[Ch0.3/kg d1–5, P40/m^2 d1–5]/4w
PETHEMA *(19)*	1988–1991	5	A	[Ch0.4/kg d5–6, P40/m^2 d1–4]/2w
IGCI-CLL01 *(8)*§	1982–1986	7	TTM ≤9	[Ch75 d1, P30 d1–7]/4w *or* [Ch15] daily
Chlorambucil versus chlorambucil plus prednisone/prednisolone				
Roswell Park *(20)*	1965–1970	—	Any	[Ch6 ± P30] daily
PETHEMA *(16)*	1988–1994	4	B	[Ch0.4/kg d5–6 ± P40/m^2 d1–4]/2w
MRC-CLL-2 *(18)*	1984–1990	8	B or C	[Ch2 d1–3 ± P40 d1–5]/m^2/4w
COP (cyclophosphamide, vincristine, and prednisone/prednisolone) versus chlorambucil				
MRC-CLL-1 *(18)*	1978–1984	15	Ip, IIp, III, or IV	[(Cy250 or 125, P40) d1–5, O1.4 dl]/m^2/4w *or* [Ch1.5/kg d1–3]/4w
FRE-CLL-80 *(21)*	1980–1985	11	B	[(Cy300, P40) d1–5, O1 d1]/m^2/4w *or* [Ch0.1/kg] daily
PETHEMA *(12)*	1978–1983	—	C	[(Cy600, O1) d6, P60 d1–5]/m^2/4w *or* [Ch0.4 d6, P60 d1–5]/m^2/2w
EST-2480 *(22)*	1980–1983	10	IIp, III, or IV	[(Cy300, P100) d1–5, O1.4 d1]/m^2/3w *or* [Ch30/m^2 d1, P80 d1–5]/2w
CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone) versus chlorambucil				
Sweden *(23)*	1982–1988	10	III or IV	[(Cy750/m^2, H50/m^2, O2) d1, P50/m^2 d1–5]/4w *or* [Ch0.4/kg d1, P75 d1–3]/2w
Danish CLL-2 *(24)*	1984–1989	7	B or C	[(Cy750, H50, O1) d1, P40 d1–5]/m^2/4w *or* [(Ch10, P40) d1–5]/m^2/4w
FRE-CLL-85 *(25)*	1985–1990	6	B	[(Cy300, H25, P40) d1–5, O1 d1]/m^2/4w *or* [(Ch0.3/kg, P40/m^2) d1–5]/4w
PETHEMA *(12)*	1987–1993	2	C	[(Cy600, H25, O1) d1, P40 d1–5]/m^2/4w *or* [Ch0.4/kg d5–6, P40/m^2 d1–4]/4w
IGCI-CLL02 *(26)*	1987–1993	2	TTM >9	[(Cy300, P40) d1–5, (O1, H25) d1]/m^2/4w *or* [Ch15] daily
CHOP versus COP				
FRE-CLL-80 *(5)*	1980–1985	10	C	[(Cy300, P40) d1–5, (O1, H25) d1]/m^2/4w *or* [(Cy300, P40) d1–5, O1 d1]/m^2/4w
Chlorambucil + epirubicin versus chlorambucil				
MRC-CLL-3 *(27)*	1990–1997	3	Ap, B, or C	[E50 d1, Ch10 d2–7]/m^2/4w *or* [Ch10/m^2 d1–6]/4w

*CALGB = Cancer and Leukemia Group B, Canada; MRC = Medical Research Council, U.K.; FRE = French Cooperative Group on CLL; PETHEMA = Spanish Cooperative Group for Hematological Malignancies Treatment; IGCI = International Society for Chemo-Immunotherapy, Vienna; Roswell Park = Roswell Park Memorial Institute, Buffalo, NY; EST = Eastern Cooperative Oncology Group Study; Sweden = Lymphoma Group of Central Sweden; and Danish = Danish CLL Study Group.

†Binet stage *(6)*: A = hemoglobin level (Hb) ≥10 g/dL, platelet count ≥100 × 10^9/L, and ≤ two areas of organ enlargement (spleen, liver or lymph nodes in neck, axillae, or groin); B = Hb ≥10 g/dL, platelet count ≥100 × 10^9/L, and ≥ three areas of organ enlargement; and C = Hb <10 g/dL or platelet count <100 × 10^9/L. Ap = stage A with at least one of the following: *(a)* constitutional symptoms attributable to the disease, e.g., pyrexia, night sweats, weight loss; *(b)* transformation to a more aggressive histology, e.g., prolymphocytic transformation with >20% prolymphocytes; *(c)* doubling time for total lymphocyte count <12 months, associated with a downward trend in the Hb and/or platelet counts; *(d)* ≥50% increase in the size of the liver and/or spleen; appearance of hepatomegaly or splenomegaly, not previously present; and *(e)* appreciable increase in lymphadenopathy (an increase in lymphadenopathy in otherwise well patients may not indicate progression). Rai stage *(7)*: I = Hb ≥10 g/dL, platelet count ≥100 × 10^9/L, and palpable lymph nodes but not spleen; II = Hb ≥10 g/dL, platelet count ≥100 × 10^9/L, and palpable spleen; III = Hb ≤10 g/dL, platelet count ≥100 × 10^9/L; IV = platelet count <100 × 10^9/L; Ip, IIp = stage I, II, respectively, and persistent downward trend in Hb or platelet count with one of the following: (i) substantial increase in physical signs, (ii) consistent upward trend in lymphocyte count, doubling within 12 months, or (iii) constitutional symptoms; TTM *(8,26)*: total tumor mass score = sum of (i) square root of the absolute number of peripheral blood lymphocytes/nL, (ii) diameter of largest palpable lymph node in cm, and (iii) extent of palpable spleen below the costal margin, in cm.

‡Ch = chlorambucil; P = prednisone/prednisolone; Cy = cyclophosphamide; H = doxorubicin; O = vincristine; E = epirubicin; kg = kilogram body weight; m^2 = square meters of body surface area; d = day; w = week; d1 = on day 1; d1–3, etc. = on days 1–3, etc.; /4w, etc. = every 4 weeks, etc.

§Excluded. *See* "Methods" section for details.

Analyses of the overall results were to be supplemented by analyses in various subgroups defined by age, sex, or disease stage. Patients in the trials of immediate versus deferred treatment all had early-stage disease [Binet et al. *(6)* stage A] and were further subdivided either by the Rai et al. *(7)* system or by splitting the Binet stage A into A' and A" (the latter comprising those with hemoglobin <12 g/dL or with a lymphocyte count of at least 30 × 10^9/L) *(4)*. Patients in the trials of combination chemotherapy versus single-agent chlorambucil were subdivided into Binet stages A, B, and C.

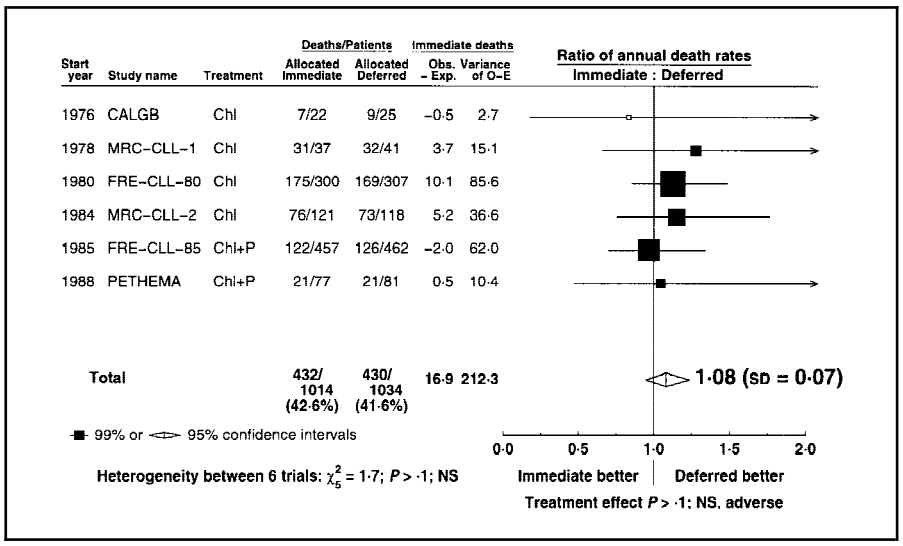

Fig. 1. Ratios of annual death rates in the trials of immediate versus deferred treatment with chlorambucil (Chl) for early-stage chronic lymphocytic leukemia (CLL). Each trial result is represented by a square, with a horizontal line indicating the 99% confidence interval. An open square (1976 CALGB trial) indicates that tabular data have been used. The overall result is represented by a diamond (whose width shows the 95% confidence interval), beside which is the ratio of the death rates and the standard deviation (SD) of this ratio. Some trials tested chlorambucil alone; others tested chlorambucil plus steroid (Chl+P [prednisone/prednisolone]). Abbreviations used to describe the included trials are as follows: CALGB = Cancer and Leukemia Group B, United States and Canada; MRC = Medical Research Council, U.K; FRE = French Cooperative Group on CLL; and PETHEMA = Spanish Cooperative Group for Treatment of Hematological Malignancies. Because of unreliable randomization, the first study results for IGCI (International Society for Chemo-Immunotherapy, Vienna)-CLL01 *(8)* (12 deaths among 38 patients with immediate versus 23 deaths among 93 patients with deferred treatment, logrank observed minus expected (O–E) = 1.71 with variance of 7.25) are excluded. NS = not statistically significant; χ^2_n = chi-squared test with n degrees of freedom; Obs = observed; and Exp = expected. Reference citations for each included study are given in Table 1. *P* values are two-sided.

Most of the randomized trials were identified through the International Workshop on CLL, but searches were also done of MEDLINE® database, clinical trial databases, meeting abstracts, and reference lists to identify all of the relevant trials that started before 1990.

For each individual patient, information was requested on his or her status at randomization (hemoglobin level, platelet count, lymphocytes as a percentage of the white blood cell count, the Binet and Rai stages, and whether there was enlargement of the spleen, of the liver, or of the lymph nodes in the neck, axillae, or groin), sex, dates of birth, randomization, and death (or last follow-up) and cause of death.

Data were checked centrally for consistency, for randomization balance over time and with respect to initial variables, and for any out-of-range values. Queries, together with tables of deaths by allocated treatment and by other patient variables, were sent back to the responsible trialists for checking and, where necessary, the data were amended. Results from the first International Society for Chemo-Immunotherapy trial *(8)* (one part of which was of early versus deferred treatment and one part of which was of high-dose versus standard chlorambucil) were not used because the randomization procedures did not appear to fulfil the criterion of balanced allocation over time.

Statistical Analysis

The combination of results from several trials does not assume that patients, treatments, or follow-up procedures in different trials are the same. Indeed, there are likely to be important differences between different studies. Hence, in the present analyses, patients in one trial are compared directly only with other patients in that same trial, thereby avoiding any unjustified assumptions about the comparability of different trials. The main analyses were of deaths from any cause and of deaths from CLL (which included deaths from an unknown cause but "censored" deaths from other cancers or any cause that was definitely unrelated to CLL or its treatment).

All survival analyses were based on the "intention to treat" principle (i.e., they were based only on the allocated treatment) and involved logrank tests and survival curves *(9,10)*, excluding only the few patients who had no follow-up information. The observed minus expected (O − E) number of deaths that was derived from logrank analysis, together with the variance (V) of (O − E), was calculated for the more heavily treated group in each trial. These results, one per trial, were then summed to give a grand total (the variance of which is the sum of the separate variances), which was then used to calculate the ratio of the death rates *(9)*. For two small trials *(11,12)*, only tabular data were available on the number of deaths and patients in each treatment arm. For these trials, O – E was calculated from the crude overall numbers of deaths in each group, but although their results could be used in the principal analysis, they could not contribute to the survival curves or subgroup analyses. Confidence intervals (CIs) given for

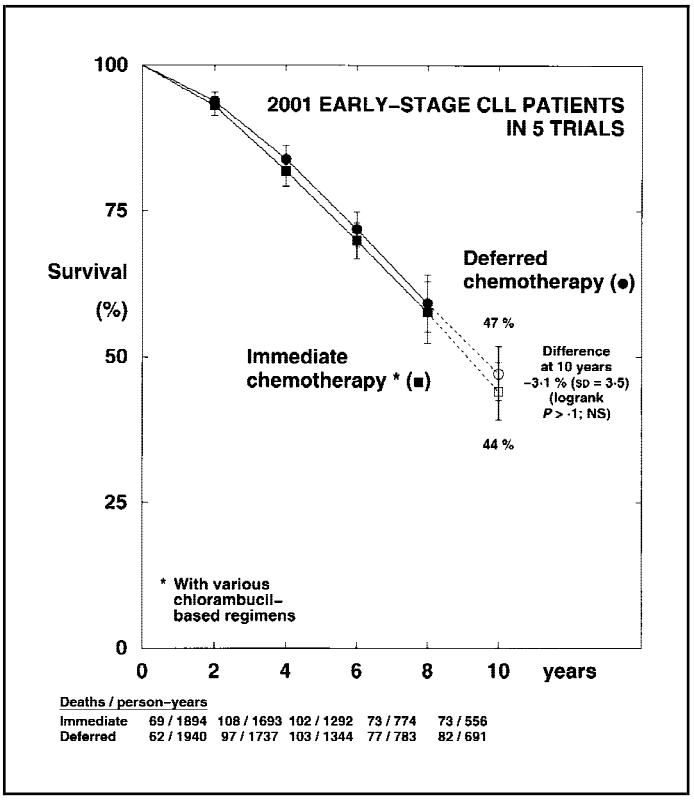

Fig. 2. Survival rates in trials of immediate versus deferred treatment for chronic lymphocytic leukemia (CLL). Because only tabular data were available for the Cancer and Leukemia Group B trial, U.S. and Canada trial *(11)*, this trial is not included in the analysis shown in the figure. The squares indicate immediate chemotherapy and the circles indicate deferred treatment. Vertical lines above and below each plotted point indicate one standard deviation (SD). Open symbols and dotted lines are used to indicate that the death rates in the last period shown are based on all deaths in or after that period. Hence, this graph displays all follow-up data, including the 66 deaths occurring beyond 10 years. Stated survival percentages have been rounded to the nearest integer, but the difference is given to one decimal point. Deaths and person-years refer to the 2-year intervals under which they are printed (except for the final period). NS = not statistically significant and logrank = logrank test. *P* values are two-sided.

overviews of several trials are 95% CIs, but CIs given for individual trial or subgroup results are 99% CIs to allow for multiple testing.

P values given throughout this article are two-tailed. Standard chi-squared tests were used to assess any heterogeneity of treatment effect between trials or with regard to age, sex, or stage. These involve the formula $\Sigma(O - E)^2/V - [\Sigma(O - E)]^2/\Sigma V$. Finally, as a global test of heterogeneity with respect to patient characteristics, the chi-squared statistics for age, for stage, and for sex were added up, yielding an approximate overall chi-square test.

RESULTS

Immediate Versus Deferred Treatment of Early-Stage Disease

Seven randomized trials of immediate versus deferred chemotherapy were identified (Table 1), involving 2210 patients. In all seven trials, the treatment involved chlorambucil, either alone or with steroids. Individual patient data were available from all but one of the studies, from which tabular results were obtained. No follow-up was available for 31 patients from four of the trials. The results of one study of 131 patients *(8)*, which were similar to those of the overall meta-analysis, were not included (*see* "Methods" section). The analysis thus involved 2048 patients from six trials (Fig. 1). Overall, there was a slightly higher death rate among patients allocated immediate chemotherapy (42.6%) than among those allocated deferred treatment (41.6%), but the excess was not statistically significant (ratio of all-cause death rates = 1.08; 95% CI = 0.95–1.24; Fig. 1). At 10 years, there was an absolute survival difference of 3% (95% CI = 4% to −10%; not statistically significant) in favor of deferring treatment (Fig. 2; 44% 10-year survival with immediate versus 47% with deferred chemotherapy).

Since these patients had early-stage disease, almost half the deaths were definitely attributed to causes other than CLL, and these non-CLL deaths appeared not to have been affected by the allocated treatment (182 deaths among 992 patients in allocated immediate treatment versus 190 deaths among 1009 patients in deferred treatment; ratio of death rates = 1.02 [95% CI = 0.83–1.25], not statistically significant; $P = .8$). Some of these non-CLL deaths were due to other cancers, but these did not appear to be related to treatment (64 in patients allocated immediate treatment versus 61 in deferred treatment). Hence, analyses that were restricted to the CLL deaths indicated a slightly greater, but still not statistically sig-

Table 2. Effects of treatment on survival in various subgroups of patients with chronic lymphocytic leukemia by age, sex, and disease stage

Subgroup*	No. of deaths/No. of patients		Statistics		Odds ratio (99% confidence interval)
			Observed minus expected No. of deaths	Variance of observed minus expected No. of deaths	
	Immediate treatment	Deferred treatment			
Age, y					
<60	81/277	71/267	5.7	37.4	1.16 (0.76–1.77)
60–69	156/384	130/366	14.3	69.0	1.23 (0.90–1.68)
⩾70	178/316	210/361	2.7	94.1	1.03 (0.79–1.34)
Sex					
Male	270/597	291/608	−3.4	138.7	0.98 (0.78–1.21)
Female	155/393	130/400	20.5	70.0	1.34 (0.99–1.82)
Binet stage *(6)*†					
Substage					
A′	255/704	296/748	−3.0	135.6	0.98 (0.78–1.22)
A″	158/272	118/248	10.8	67.6	1.17 (0.86–1.61)
Rai stage *(7)*					
0	187/538	166/518	7.8	86.9	1.09 (0.83–1.44)
I	128/283	136/309	7.9	63.9	1.13 (0.82–1.56)
II	72/121	82/133	2.3	36.1	1.07 (0.70–1.64)
Sum of four heterogeneity tests: $\chi^2_6 = 7.6$; not statistically significant ($P = .3$)‡					
	Combination chemotherapy	Chlorambucil			
Age, y					
<60	198/338	186/338	7.2	93.3	1.08 (0.88–1.32)
60–69	225/371	222/354	−4.2	107.1	0.96 (0.80–1.16)
⩾70	168/222	188/269	9.0	82.7	1.11 (0.90–1.38)
Sex					
Male	395/628	408/648	0.3	197.5	1.00 (0.87–1.15)
Female	159/262	151/275	6.4	73.6	1.09 (0.87–1.37)
Binet stage *(6)*					
A	65/113	77/132	−8.4	32.8	0.78 (0.55–1.09)
B	325/517	343/553	2.2	164.4	1.01 (0.87–1.18)
C	200/299	177/279	14.8	89.2	1.18 (0.96–1.45)
Sum of three heterogeneity tests: $\chi^2_5 = 5.9$; not statistically significant ($P = .3$)‡					

*Subgroup data were not available for the two trials *(11,12)* supplied as tabular data only, and information regarding some variables is missing for some patients; hence, the subgroup totals are not identical. For a description of disease staging, please refer to the footnotes to Table 1. All *P* values are two-sided.

†Binet stage A is subdivided into substage A′ and substage A″ comprising those with hemoglobin level <12 g/dL and with a lymphocyte count of at least 30×10^9/L, respectively.

‡χ^2_6 and χ^2_5 are chi-squared tests on 6 and 5 *df*, respectively.

nificant, advantage for deferred treatment (immediate treatment versus deferred treatment; ratio of CLL death rates = 1.14; 95% CI = 0.95–1.37; not statistically significant; $P = .1$).

Analyses of overall mortality in various subcategories of age, sex, substage, or Rai stage did not show any clearly heterogeneous treatment effects (overall heterogeneity test: $\chi^2_{6\ df}$ (chi-squared test on six degrees of freedom) = 7.6; not statistically significant; $P = .7$; upper part of Table 2). Considered in isolation, the heterogeneity with respect to sex just achieves conventional significance ($\chi^2_{1\ df} = 4.7$; $P = .03$), but when appropriate allowance is made for there being four such tests, this ceases to be significant, and it should not be concluded from such data that immediate treatment is good for females but not for males. In every subgroup the confidence intervals for the death rate ratios included 1.0, indicating no significant survival advantage from starting treatment immediately but no significant hazard from doing so.

Combination Chemotherapy Versus Single-Agent Chemotherapy With Chlorambucil

Only three trials, involving 424 patients, of whom 19 had no follow-up, involved randomized allocation of the addition of a steroid to chlorambucil (Table 1). A meta-analysis of the results of these three trials did not suggest that the steroid affected patient survival (ratio of death rates with versus without steroid = 0.98; 95% CI = 0.77–1.25), but the total number of patients randomized in these trials is too small to say definitely whether or not it does so. In all other comparisons, however, these two treatments will be considered together and will be referred to as "chlorambucil," not mentioning the steroid explicitly.

Ten trials, involving 2035 patients, mostly with Binet stage B or C disease, randomly assigned patients between combination chemotherapy and chlorambucil. Of these 10 trials, four (for one of which only tabular data were available) used COP, five used CHOP, which contains the anthracycline doxorubicin, and one used chlorambucil plus epirubicin (*see* Table 1 for definitions of these drug combinations). Thirteen patients had no follow-up, so 2022 patients are included in the analysis (Fig. 3).

Overall, combination chemotherapy did not appear to be any better than chlorambucil (ratio of death rates for combination chemotherapy versus chlorambucil = 1.01; 95% CI = 0.90–1.13; Fig. 3). The survival curves show no evidence of a difference at any time (Fig. 4), the survival at 5 years being 48% with combination chemotherapy versus 48% with chlorambucil. The 95% CI for the difference between these two percentages was −6% to 5%, so it is possible that a small net benefit or hazard exists, but

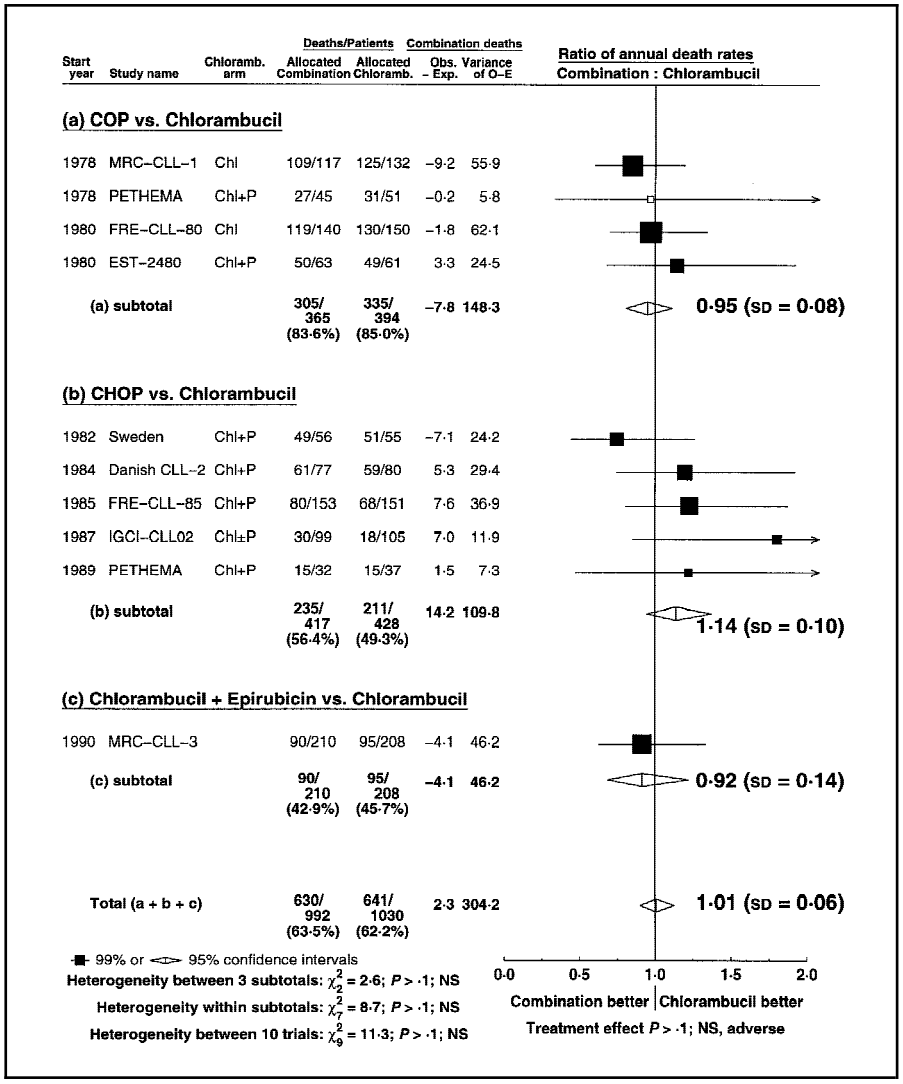

Fig. 3. Ratios of annual death rates in the trials of combination chemotherapy versus chlorambucil for chronic lymphocytic leukemia (CLL). Each trial result is represented by a square, with a horizontal line indicating the 99% confidence interval. An open square (1978 PETHEMA trial) indicates that tabular data have been used. The overall result is represented by a diamond (whose width shows the 95% confidence interval), beside which is the ratio of the death rates and the standard deviation (SD) of this ratio. COP = cyclophosphamide and vincristine, plus prednisone/prednisolone. CHOP = COP plus doxorubicin. NS = not statistically significant; χ^2_n = chi-squared test with n degrees of freedom; Chloramb. = chlorambucil; Obs. and O = observed; and Exp. and E = expected. *P* values are two-sided.

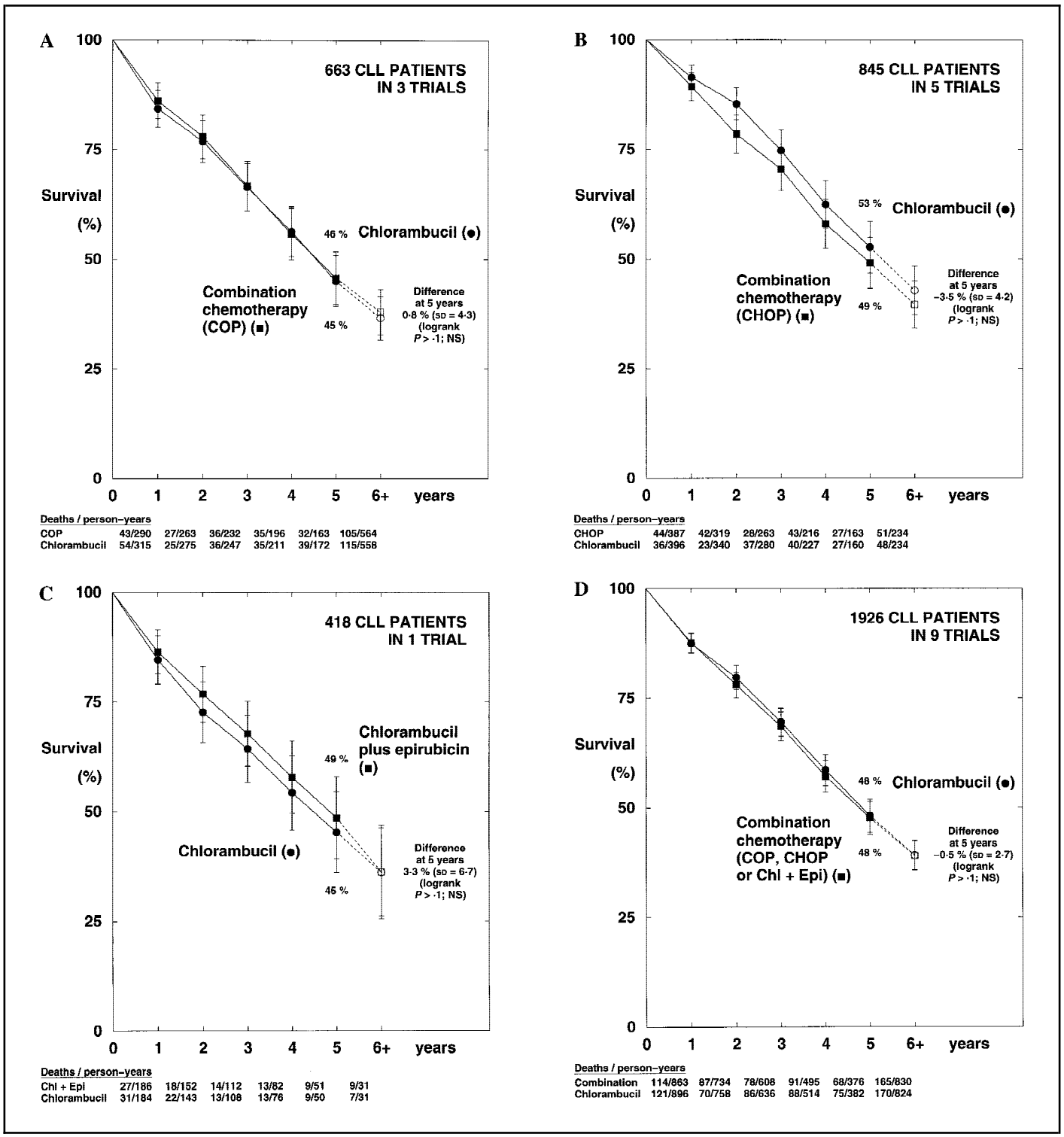

Fig. 4. Survival rates in trials of combination chemotherapy versus chlorambucil for chronic lymphocytic leukemia (CLL).The format is similar to that shown in Fig. 2, with the squares indicating combination chemotherapy and circles indicating chlorambucil treatment. **A**) Cyclophosphamide and vincristine plus prednisone/prednisolone (COP) versus chlorambucil. **B**) COP plus doxorubicin (CHOP) versus chlorambucil. **C**) Chlorambucil plus epirubicin versus chlorambucil *(27)*. **D**) Any combination (COP, CHOP, or chlorambucil [Chl] plus epirubicin [Epi]) versus chlorambucil. NS = not statistically significant; SD = standard deviation; and logrank = logrank test. Deaths and person-years refer to the 1-year interval under which they are printed (except for the final period). *P* values are two-sided.

there cannot be a large difference. There was no significant heterogeneity of treatment effect between trials or between the trials of COP versus chlorambucil (death rate ratio = 0.95; 95% CI = 0.81–1.11; not statistically significant; $P = .5$), of CHOP versus chlorambucil (death rate ratio = 1.14; 95% CI = 0.94–1.37; not statistically significant; $P = .2$), and of chlorambucil plus epirubicin versus chlorambucil (death rate ratio = 0.92; 95% CI = 0.69–1.22; not statistically significant; $P = .5$). Thus, there is no evidence from these trials that early inclusion of an anthracycline improves the 5-year survival: Indeed, the

overall survival was slightly, although not statistically significantly, worse with the anthracycline-containing regimens than it was with chlorambucil (overall mortality: 325 deaths among 627 patients allocated anthracycline versus 306 deaths among 636 patients allocated chlorambucil, death rate ratio = 1.07; 95% CI = 0.91–1.25).

Since most of these patients had advanced disease, fewer than a quarter of their deaths (22%) were attributed to causes other than CLL. Because these non-CLL deaths did not appear to be related to the treatment allocation, omission of them made little difference to the overall results (ratio of CLL death rates for combination chemotherapy versus chlorambucil = 0.96; 95% CI = 0.84–1.09).

Analyses within subgroups defined by age, sex, and Binet stage did not show any clearly different treatment effect in any particular category of patient; again, in every subgroup, the CIs for the death rate ratio included 1.0 (Table 2); i.e., they included the possibility that first-line treatment with combination chemotherapy and with single-agent chlorambucil has similar effects on survival. (Even for patients with stage C disease, these trials provided no evidence in favor of the early use of combination therapy: *see* final line of Table 2.)

Discussion

The two largest trials of immediate versus deferred treatment were both from the French collaborative group *(13,14),* which provided the first substantial randomized evidence that the cytotoxic treatment of early-stage disease can safely be deferred. The present overview, which includes updated results from these two French trials plus results from several smaller studies, confirms this conclusion, but does not confirm the suggestion that this may be because of an adverse effect of prolonged chlorambucil on non-CLL deaths *(13).* Although patients with early-stage CLL have a relatively good prognosis, about half will eventually die of their disease, and the factors in the Rai and Binet staging systems (or other prognostic factors, such as the doubling time of the lymphocyte count) can help identify those most likely to do so. But, although it is possible that, among patients with early-stage disease, some with a relatively poor prognosis could be identified who might benefit from immediate treatment, there is nothing in the currently available trial results to suggest this. Indeed, it may be that there are also some patients among those with more advanced disease who do not need much immediate chemotherapy. If, however, better drugs were available (such as, perhaps, the purine analogues that are now producing improved responses in advanced disease) *(15–17),* then the issue of when to start the treatment of early-stage disease might need to be reconsidered.

The present meta-analysis of the results from the trials of combination chemotherapy versus chlorambucil (with or without steroids) suggests no survival benefit with the chemotherapy combinations that were used in these trials, irrespective of whether the combination included an anthracycline. The first trial [French CLL-80 *(4)*] that addressed the effect of an anthracycline compared the two different combination chemotherapy regimens (CHOP versus COP) and observed 27 deaths among 36 patients versus 33 deaths among 34 patients, respectively (logrank observed minus expected = −11.0 with variance 13.4; $P = .003$). The apparent superiority of CHOP in that particular study must, however, be largely or wholly due to the play of chance, for the trial involved only 70 patients (with only one survivor among the 34 allocated COP), recruitment to it was stopped early on the basis of an interim analysis, and the large apparent difference in death rates in that one small trial is not compatible with the lack of superiority of CHOP shown by the indirect evidence that is now available from other trials that involved much larger numbers of patients (Fig. 3).

None of the combination chemotherapy regimens in these trials produced a high rate of complete response, and theoretically one might expect improved survival with treatments that give higher response rates. The current randomized trials of purine analogues have not yet provided reliable direct evidence as to whether the early use of such drugs will improve long-term survival, because they have not yet involved sufficient numbers of patients and sufficiently long follow-up.

In terms of survival, the trials reviewed in this article support a conservative treatment strategy for CLL: i.e., no immediate chemotherapy for most patients with early-stage disease and single-agent chlorambucil as the first line of treatment for most patients presenting with, or progressing to, advanced disease, with no evidence of additional benefit from early inclusion of an anthracycline. This strategy will, however, need to be reconsidered as more mature results become available from trials of other agents.

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NOTES

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