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Hydroxyurea versus busulphan for chronic myeloid leukaemia: an individual patient data meta-analysis of three randomized trials

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Summary. Although interferon alpha (IFN) has been shown to prolong survival in chronic myeloid leukaemia (CML), it cannot be used in all patients. Reliable evidence on the relative benefits of busulphan and hydroxyurea is of value in treating those patients who will not receive interferon. Data for each individual patient was sought from trials which randomized patients with CML to hydroxyurea vs. busulphan. Intention-to-treat stratified log rank survival analyses were performed, reporting two-sided *P*-values. Data were collected on 812 patients in the three trials identified. In the group of 690 patients with confirmed Philadelphia chromosome (Ph)-positive CML, survival at 4 years was 45·1% with busulphan and 53·6% with hydroxyurea, an absolute benefit of 8·5% (95% confidence interval 0·1–16·9; logrank $P = 0·01$ over 4 years). There seemed to be no further benefit for hydroxyurea in later years, but there was no apparent delayed adverse effect either. The difference between hydroxyurea and busulphan was not statistically significantly different from the overall result in any subgroup. Survival of patients with Ph-positive CML is better with hydroxyurea treatment than with busulphan.

Keywords: chronic myeloid leukaemia, meta-analysis, randomized, hydroxyurea, busulphan.

Although interferon alpha (IFN)-based therapy may be the treatment of choice for most patients with chronic myeloid leukaemia (CML) (Chronic Myeloid Leukaemia Trialists' Collaborative Group, 1997), there are still many patients for whom some other treatment might be chosen. The reasons for this choice include the minimization of side-effects, the preservation of quality of life and the desire to avoid IFN before transplantation because of suggested adverse effects (Morton *et al*, 1998; Hehlmann *et al*, 1999). Thus, the relative effect of therapies other than IFN remains an important question.

An individual patient data meta-analysis of the randomized trials of IFN vs. chemotherapy for CML showed that IFN improved the survival of Philadelphia chromosome (Ph)-positive patients compared with hydroxyurea or busulphan (Chronic Myeloid Leukaemia Trialists' Collaborative Group, 1997). The randomized comparisons showed that IFN improved outcome compared with either type of chemotherapy, but patients treated with hydroxyurea seemed to do better than those treated with busulphan. However, this indirect comparison of busulphan and hydroxyurea is subject to many potential biases. For example, there were differences in the types of patient studied, the treatment centres and the duration of treatment. To obtain a reliable estimate of the relative effects of these two chemotherapies on survival, data from randomized trials directly addressing this question were needed.

At the time of the IFN meta-analysis, data were available from two of the three trials known to have directly compared busulphan with hydroxyurea. Data from the unpublished Swedish trial were not available and so the results for this comparison could not be regarded as definitive at that time.

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PATIENTS AND METHODS

Patients. Identification of relevant trials and data collection and checking methods were the same as those used in the IFN meta-analysis (Chronic Myeloid Leukaemia Trialists' Collaborative Group, 1997). Three trials were identified (Table I) and data are now available for all of them. The main analyses are confined to Ph-positive patients (690 patients), but separate results are also given for those who

Table I. Randomized trials of hydroxyurea vs. busulphan.

Study	Reference	Hydroxyurea		Busulphan		Median years follow-up of survivors
		Initial daily dose	Target WBC	Initial daily dose	Target WBC	
German-CML-1	Hehlmann *et al* (1993)	40 mg/kg	5–15	0·1 mg/kg	< 20	10
MRC-CML-3	Allan *et al* (1995)	1·5–2·0 g	4–20	4 mg	4–20	6
Swedish CML Trial	Unpublished observations	30 mg/kg	10–20	0·1 mg/kg	10–20	10

were Ph negative (84 patients) or had unknown Ph status (38 patients).

Statistical analyses. Intention-to-treat log rank survival analyses were used to obtain the observed (O) and expected (E) numbers of deaths in the hydroxyurea-allocated group and the associated variance (Var) for each trial. The sum of these statistics over the three trials was used to calculate the estimated death-rate ratio {exp[(O–E)/Var]} (Early Breast Cancer Trialists' Collaborative Group, 1992). All *P*-values are two-sided.

RESULTS

Figure 1 shows the results among Ph-positive patients for each of the three trials and the combined result. There is an overall non-statistically significant reduction in the annual death rate of 13% [95% confidence interval (CI) = −3 to 26; $P = 0{\cdot}1$]. There was no statistically significant difference between the results of each trial. If the follow-up of patients who had a bone marrow transplant in chronic phase was censored at the time of their transplant, the estimate of the effect on the annual death rate was only slightly changed at 16% (95% CI = 0–29; $P = 0{\cdot}06$).

Figure 2 shows the effect on survival. At 4 years, survival was 45·1% with busulphan and 53·6% with hydroxyurea, an absolute difference of 8·5% (95% CI = 0·1–16·9; logrank $P = 0{\cdot}01$ over 4 years). At 10 years, the absolute difference was 2·3% (95% CI = −4·0 to 8·7). This smaller absolute difference was not as a result of any adverse effect over the later years, but rather as a result of the fact that there was no additional benefit. For example, if the survivals in two groups are 60% and 50% at a certain time (an absolute difference of 10%) and the annual event rate is 20% in each group thereafter, then the survivals after a further 3 years will be 31% and 26% respectively (an absolute difference of only 5%). During the first 4 years the statistically significant reduction in the annual death rate was 24% (95% CI = 6–38), while over later years there was a non-significant increase of 6% (95% CI = 8% reduction to 37% increase) (Fig 3).

Figure 3 shows the results for the different types of patient and for different periods of follow-up. The numbers of Ph-negative and Ph-status unknown patients were too small for these to be informative, but the data are given here for completeness. Analyses are also shown within Sokal stage (Sokal *et al*, 1984), age and sex subgroups for Ph-positive patients. There was no good evidence that the apparent benefit of hydroxyurea was not present in any of the subgroups. Reduction in the death rate with hydroxyurea seems to be greatest over the first few years, with little additional benefit, but no adverse effect, in later years.

DISCUSSION

For patients with Ph-positive CML the inclusion of all the relevant randomized evidence indicates that with the strategies used in these protocols, hydroxyurea as the primary treatment improves survival over the first few years compared with busulphan. It would seem beneficial to use hydroxyurea rather than busulphan for all patients not receiving IFN, as there is no evidence that busulphan treatment is better for any particular patient subgroup.

In addition, busulphan has an idiosyncratic tendency to

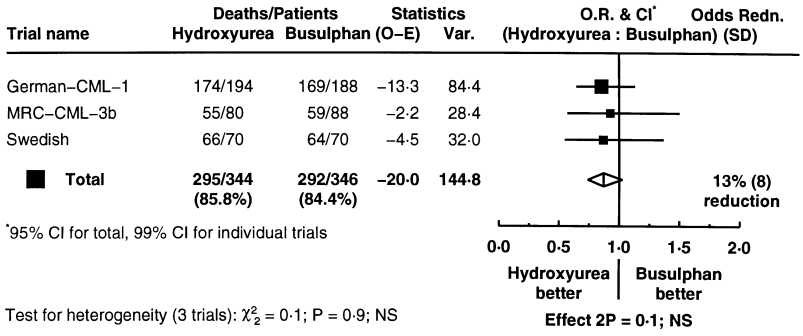
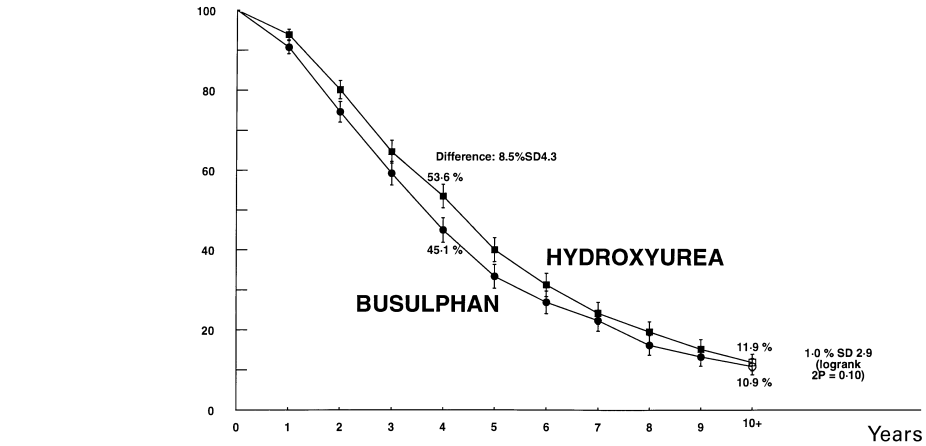


Fig 1. Ratios of annual death rates in the trials of hydroxyurea vs. busulphan in Philadelphia-positive chronic myeloid leukaemia. Each trial result is represented by a square and a horizontal line indicating the 99% confidence interval. The overall result is represented by the diamond whose width shows the 95% confidence interval. SD, standard deviation; O–E, log rank observed minus expected; Var, variance of O-E.



Deaths/person-years:

Year	1	2	3	4	5	6	7	8	9	10+
Hydroxyurea	21/338	47/229	52/243	38/204	46/158	29/113	22/85	13/61	11/43	16/66
Busulphan	33/337	56/284	53/229	50/178	37/125	19/94	13/73	17/52	6/33	8/43

Fig 2. Survival rates in the overview of hydroxyurea vs. busulphan in Philadelphia-positive chronic myeloid leukaemia. The descriptive survival curves are calculated from the log rank observed minus expected and its variance in each separate year for each trial. Vertical lines indicate one standard error above or below each plotted point.

cause severe marrow aplasia that may be fatal and there is also an association with pulmonary fibrosis (Haut *et al*, 1969; Weatherall *et al*, 1969). Furthermore, alkylating agents such as busulphan are thought to carry a higher leukaemogenic risk than hydroxyurea when administered to patients with other myeloproliferative disorders (Najean *et al*, 1996; Fruchtman *et al*, 1997). We can speculate that this might be one reason why the survival rate in busulphan-treated patients with chronic myeloid leukaemia is lower than the survival rate with the use of hydroxyurea alone, owing to earlier blast transformation.

If patients are receiving IFN, the question of whether hydroxyurea or busulphan will further improve survival remains a topic for research. However, two recently reported

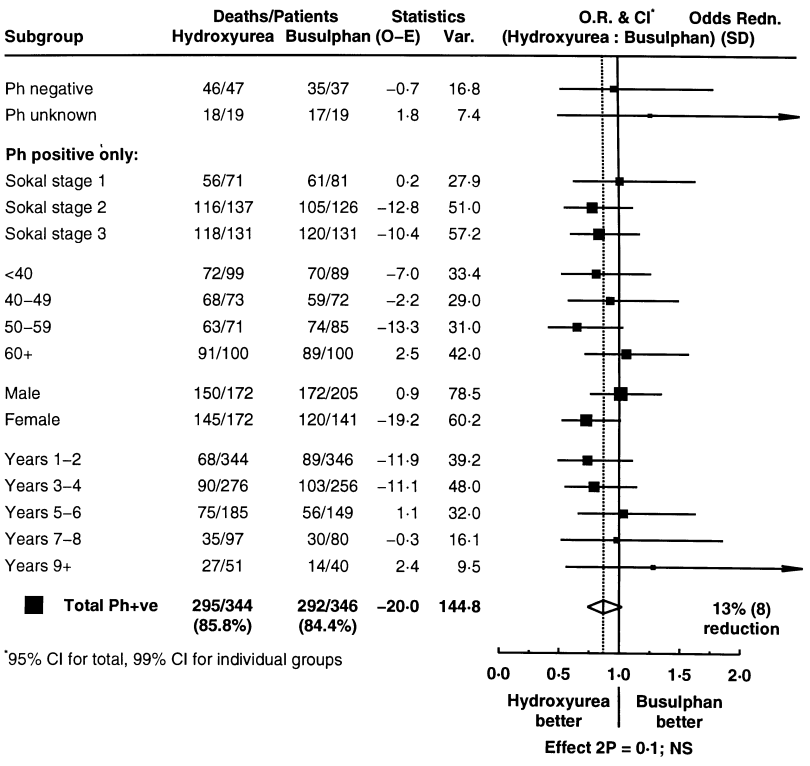


Fig 3. Ratios of annual death rates in the overview of hydroxyurea vs. busulphan in chronic myeloid leukaemia, subdivided by patient characteristics and years since randomization. Ph, Philadelphia chromosome.

trials have suggested that the addition of cytarabine to IFN improves survival in comparison with IFN alone (Guilhot *et al*, 1997; Tura and Italian Cooperative Study Group on CML, 1997). One small randomized study comparing interferon combined with hydroxyurea or cytarabine gave similar survival rates in the two arms (Giles *et al*, 1999). Therefore, as hydroxyurea improves survival, the combination of hydroxyurea and IFN might also be better than either drug given alone.

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