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Original article

Cost-effectiveness of interferon in chronic myeloid leukaemia: Analysis of four clinical studies

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Summary

Background: Analysis of published survival curves can be used as the basis for incremental cost-effectiveness analyses in which two treatments are compared with one another in terms of cost per life-year saved. In patients with chronic myeloid leukaemia in chronic phase, long-term treatment with α-interferon has been reported to improve survival in comparison with standard treatments with cytotoxic drugs. To assess the pharmacoeconomic profile of interferon treatment in terms of cost per life-year gained, we conducted an incremental cost-effectiveness analysis.

Patients and methods: The clinical material utilised in our analysis derived from four published randomised trials comparing interferon vs. busulphan or hydroxyurea. The Gompertz model was used to estimate the total lifetime values of patient-years of subjects receiving interferon in comparison with subjects given a standard cytotoxic treatment.

Results. Our primary analysis showed that maintenance treatment with interferon improved survival expectancy by 37 to 93 discounted years for every 100 patients. The incremental cost-effectiveness ratio of interferon vs. cytotoxic therapy ranged from $93,000 to $226,000 per life-year gained (discounted costs per discounted years). A secondary analysis showed that the dose of interferon had significant influence on the cost-effectiveness ratio. Because our literature search identified a fifth study that showed an extremely favourable outcome using interferon but that was not included in our primary analysis due to its design, we conducted another secondary analysis based on these five studies that, however, confirmed the results of the primary analysis.

Conclusions: Our study indicates that an unselected long-term treatment with interferon implies an unfavourable cost effectiveness ranking in comparison with data of cost per life-year gained which had previously been obtained from other types of medical intervention.

Key words: chronic myeloid leukaemia, cost-effectiveness analysis, interferon, pharmacoeconomics

Introduction

In patients with chronic myeloid leukaemia in chronic phase, administration of α-interferon (IFN) as maintenance treatment has been reported to improve survival in comparison with standard treatments with cytotoxic drugs such as busulphan or hydroxyurea [1–7].

In the present study, we assessed the pharmacoeconomic profile of this maintenance treatment with IFN in terms of cost per life-year gained. For this purpose, we conducted an incremental cost-effectiveness analysis in which we used the clinical data of four controlled clinical trials published in recent years [1–4].

Patients and methods

Study design and perspective of the cost-effectiveness analysis

In pharmacoeconomic analysis, costs and benefits vary with the perspective of the relevant study, and the analysis can in fact be constructed to reflect the viewpoint of society as a whole, those covering the financial costs, health care providers, or patients. In the present study, costs were assessed from a social perspective [8–18] and were considered to reflect only the expenditure of health care resources (i.e., direct costs), not indirect expenses such as wages or productivity lost because of illness or death.

Our study quantified costs in monetary units and benefits in terms of number of life-years gained and was therefore a typical cost-effectiveness analysis. The analysis compared maintenance treatment with IFN vs. standard cytotoxic therapy and was aimed at determining an incremental cost-effectiveness ratio (ratio of incremental cost and incremental benefit, where incremental cost is the cost difference between treated patients and controls and incremental benefit is the lifetime difference in life-years between the two patient groups). Our work was planned as a cost-effectiveness study in which both cost and effectiveness were estimated using a lifetime temporal horizon [8, 14–20] and without introducing any assessments of quality of life. The primary analysis evaluated a baseline scenario whereas two sensitivity analyses tested the effect of varying the dose of IFN (which was a key factor influencing the cost-effectiveness ratio) and the data-base of clinical trials included in our study.

Clinical data included in the analysis

Our primary analysis utilised four randomised controlled clinical trials published by Allan et al. [1] (English trial), Tura et al. [2] (Italian trial), Hehlmann et al. [3] (German trial), and Ohnishi et al. [4] (Japanese

Table I. Characteristics of the four trials included in our pharmacoeconomic analysis.[a]

Study	Type of α-IFN (no. of pts)	Reference treatment (no. of pts)
German trial	Recombinant IFN (133)	Busulphan (186) or hydroxyurea (194)
English trial	Lymphoblastoid IFN (293)	Busulphan or hydroxyurea (294)
Italian trial	Recombinant IFN (218)	Busulphan or hydroxyurea (104)
Japanese trial	Recombinant IFN (80)	Busulphan (79)

[a] The fifth trial (American trial), which was introduced in our second sensitivity analysis, included 41 patients in the recombinant IFN group and 122 historical controls treated with hydroxyurea.

trial), while a non-randomised study using historical controls, conducted by Schofield et al. [5] (American trial), was included in our second sensitivity analysis.

The designs of the four controlled studies (German, English, Italian, and Japanese trials; see Table 1) were very similar (total number of patients enrolled in these studies = 724 in the IFN groups vs. 857 in the control groups). The main end-points of these studies included survival (available in all studies) and progression-free survival (available in the Italian and Japanese studies).

Incremental cost-effectiveness analysis based on survival data

Our cost-effectiveness analysis conformed to a classic scheme in which a new, more effective and more costly treatment (IFN) is compared with a less expensive, standard treatment (busulphan or hydroxyurea). The following steps were followed separately for each of the four studies:

1. Estimates were obtained of the cost of treating 100 patients with either IFN or cytotoxic agents, and the incremental cost was then defined as the difference between these two amounts. Because of the incremental design of our analysis, the cost sources that were thought to be identical between the two patient groups were disregarded. In particular, long-term follow-up costs (excluding the costs of either IFN or cytotoxic therapy) were assumed to be identical.
2. The published survival curve of patients who received IFN was analysed and, in particular, the actuarial percentages of survival at the various timepoints of the follow-up were determined from the published graph. These survival percentages were used to calculate the total area under the survival curve (AUC_{IFN}) from zero time to infinity (Figure 1) using a weighted least-squares procedure of survival curve-fitting. This total area was estimated as the sum of the area directly measured in the trial (i.e., area from zero time to the last timepoint of the follow-up) plus the extrapolated right tail (i.e., area from the last point of the follow-up to infinity). Both of these components of the total area were determined according to the Gompertz function using the parameters generated by survival curve fitting (see below).
3. The survival curve of patients who received the cytotoxic treatment was analysed by the same procedure described for patients given IFN. In this case, the estimate yielded the value of $AUC_{no\text{-}IFN}$.
4. The incremental clinical benefit deriving from IFN in comparison with the standard cytotoxic treatment was calculated as the difference of AUC_{IFN} minus $AUC_{no\text{-}IFN}$ (weighted for the different size of the two patients groups and normalised to a population of 100 patients). This difference is an estimate of the number of patient years gained for every 100 patients using IFN rather than a standard cytotoxic therapy.
5. The incremental cost-effectiveness ratio (expressed on the basis of the cost per life-year gained) was calculated by dividing the incremental cost by the incremental benefit.

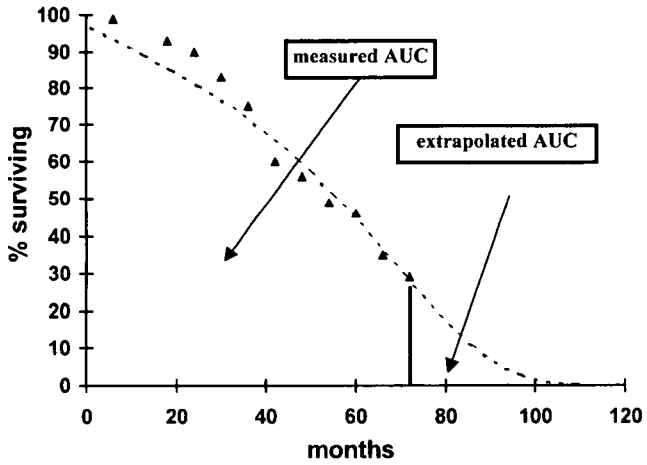

Figure 1. The least-squares fit of the trial's survival percentages (triangles) to the Gompertz function renders it possible to determine the whole survival curve as a mathematical function from time zero to infinity (dotted line). The area under the survival curve can be split into a first component (measured AUC), which corresponds to the follow-up duration of the trial, and a second component (extrapolated AUC), which corresponds to a survival prediction after the period over which the experimental data were available. The survival curve presented in this figure refers to the control group of the Italian trial.

Survival curve fitting and area estimates

The Gompertz function [8, 14–20] was used to describe the time-course of a survival curve. Its equation is as follows:

$$SP = 100\, s^t g^{c^t}$$

where: SP is the survival percentage in the survival curve; t is time; s, g, and c are the three constants of the function. In our curve fitting procedure, the numerical values of the SP-*versus*-t data pairs of the survival curve were estimated from the published graph by careful measurement [21–23]. Then, a non-linear weighted least-squares iterative fit was started to determine the best-fit values for the three model parameters (i.e., s, g, and c). In this computerised fit, the input parameters were the SP-vs-t data pairs while the output parameters were the best-fit values of s, g, and c. Our software generated an index of the goodness of fit [14–18] (root mean squared error, RMSE, expressed as a percent number) that represents the mean deviation between experimental and fitted values of SP (see Figure 1). Optimal values of RMSE should be less than 10%.

Estimates of areas under the survival curve were carried out by standard numerical integration. All mathematical calculations were performed using a specific microcomputer program [20].

Estimation of dosage and cost of the treatments with interferon or cytotxic agents

The dose of IFN actually given to the patients enrolled in the four clinical trials was estimated on the basis of the information presented in the respective articles. The cost in the US of recombinant α-interferon is about $10 per MU and the price of the drug in Europe is very similar; hence, all economic evaluations were based on this value. The cost of IFN administration, lab tests and outpatient visits to monitor IFN therapy was derived from published information [17].

The four trials did not provide sufficient details on the cumulative doses of busulphan or hydroxyurea per patient. Quantification of the doses actually administered was hampered by the intermittent nature

of therapy and by the fact that dosages were often individualised on the basis of leukocyte counts. The cost of standard cytotoxic treatment with busulphan or hydroxyurea is about 50- to 100-fold lower than the corresponding cost of IFN. Thus, the importance of precisely determining the cost of cytotoxic agents was thought to be marginal. These costs were approximated by assuming that the expenditure was $2 per patient per day or $14 per week (as reported by Hehlmann [3]) and that the therapy was given daily to all patients.

Discounting costs and benefits

In cost-effectiveness analyses, conventional practice [24] suggests the discounting of both costs and benefits, using an annual discount rate of 3% or 5%, and our study employed this discounting scheme in all analyses (annual rate = 5%).

Sensitivity analysis

Our first sensitivity analysis was aimed at testing the pharmacoeconomic consequences of different levels of IFN dosage and was based on a simplified meta-analysis of the clinical data of the four randomised clinical trials. This sensitivity analysis varied the costs of IFN, but assumed that the size of the effectiveness was not dose-dependent. The meta-analytic estimates of effectiveness were determined by calculating a pooled value of both AUC_{IFN} and $AUC_{no\text{-}IFN}$ from the trial-specific AUC values using a series of equations previously reported by Simes et al. [25] (Simes' Method A: last four equations on p. 25 of the Simes article; Simes' Method B: first two equations on p. 25). This meta-analysis allowed us to consider the effect of varying the dosage of IFN from 10 to 60 MU per patient per week. The costs per life-year gained related to the various dose levels were computed assuming 100% compliance with no discontinuations of IFN and a cost of $100 per week for interferon administration, lab tests, increased need for outpatient visits.

Because our literature search identified a fifth study (by Schofield et al. [5] and denoted herein as the American trial) showing an extremely favourable outcome using interferon, but which was not included in our primary analysis due to its design, we conducted a second sensitivity analysis that estimated the cost per life-year gained on the basis of the clinical results of these five studies

Finally, because our primary evaluation was based on a separate analysis of four situations that differed from one another in important aspects influencing cost and/or effectiveness (e.g., type and dosage of IFN, rates of compliance, clinical response to IFN, etc.), further sensitivity analyses were felt to be unnecessary.

Results

Survival curve fitting and estimation of effectiveness

The first phase of our analysis of the survival curves of the various clinical trials was the estimation of the survival percentages from the published graphs. On the basis of this information, our fitting procedures yielded the results outlined in Table 2. Each fit is identified by a code which is used in Appendix 1 to provide more details on the various Gompertz parameters.

Most of these fits were excellent, as demonstrated by the generally low RMSE values (see column 5 in Table 2). The extrapolated right tails (which, by definition, are estimated less precisely) also contribute relatively little to the respective total values of AUC (see column 6). Figure 2 presents an example of least-squares fit based on the Gompertz model; the data refer to the survival curves of the Italian study.

Costs in the patient groups treated with IFN or cytotoxic agents

Table 3 summarises our estimation of the costs related to IFN therapy (further details on this point are presented in Appendix 2). The discounted values of lifetime cost ranged from about $5,083,000 (English trial) to $17,532,000 (Japanese trial) for every 100 patients. Table 4 (column B) shows the results of our calculations concerning lifetime drug costs in patients receiving cytotoxic treatment. Inter-study variations in these data were very small.

Table 2. Lifetime values of survival in patients treated with IFN or with cytotoxic agents in the four controlled studies included in our analysis.[a]

Study	Lifetime survival (undiscounted patient months per 100 patients)	Lifetime survival (discounted patient months per 100 patients)	Goodness of fit (RMSE value, %)[b]	Contribution of extrapolated right tail to total AUC (%)[b]	Fit code (see Appendix)
Patients treated with interferon					
German trial	5958	5184	9.7	6.1	1
English trial	5839	5089	3.4	15.5	2
Italian trial	6721	5821	2.8	16.0	3
Japanese trial	6079	5353	6.2	14.7	4
Patients treated with busulphan or hydroxyurea					
German trial (busulfan)	4643	4119	8.3	2.8	5
German trial (hydroxyurea)	5638	4943	15.1	0.6	6
English trial	5478	4643	5.1	24.3	7
Italian trial	5261	4699	6.6	6.5	8
Japanese trial	4931	4439	4.8	7.6	9

[a] In the American trial (included only in the second sensitivity analysis), the values of number of patients, lifetime undiscounted survival, lifetime discounted survival, goodness of fit, RMSE, and contribution of extrapolated right tail to total AUC were 41, 14238 mos, 9106 mos, 12.3%, and 28.3%, respectively, in the IFN Group (Fit code = 10) and 122, 4735 mos, 4108 mos, 8.2%, and 0.1%, respectively, in the control group (Fit code = 11).

[b] From the undiscounted analysis.

Table 3. Dosage and costs in the patient group treated with IFN.[a]

Study	Target dose per patient (MU per week)	Correction factor (%) to account for non-compliance and/or dosage individualisation	'Corrected' lifetime dose per patient (MU per week)	(A) Cost of IFN given at 'corrected lifetime dose' ($ per week)	(B) Cost of IFN administration ($ per week)[b]	(C) Miscellaneous sources of cost (cost source, $ per week)	Total of A + B + C ($ per week)	Patient-weeks of lifetime IFN administration (undiscounted value normalised to 100 patients)[c]	Lifetime cost per 100 patients	
									Undiscounted ($)	Discounted ($)
German trial	61 SC[d]	59.5%[e]	36.3[f]	363	70	Lab tests, 20[g] Outpatient visits, 20[h]	473	12844 (estimated from data reported in Hellmann's Figure 6a, fit code = 12)	6,075,212	5,294,289
English trial	21 to 84 SC	-[i]	22 6	226	70	Lab tests, 20[g] Outpatient visits, 20[h]	336	17268 (estimated from specific data reported in Allen's Table 6, fit code = 13)	5,802,048	5,083,008
Italian trial	63SC	83%[e]	52	520	70	Lab tests, 20[g] Outpatient visits, 20[h]	630	29991 (estimated from progression-free survival curve of Figure 2 in Tura's article, fit code = 14)	18,894,330	16,085,160
Japanese trial	63 SC	83%[j]	52	520	70	Lab tests, 20[g] Outpatient visits, 20[h]	630	36980 (estimated from progression-free survival curve of Figure 2 in Ohnishi's article, fit code = 15)	23,297,820	17,532,060

Abbreviation: SC by subcutaneous route.

[a] The same data for the American trial are the following: target SC dose per patient = 10 4 MU per week; correction factor on dosages = 100%; 'corrected' lifetime dose per patient = 10.4 MU per week; (A) = $104; (B) = $30; (C) = $20; A + B + C = $154; Method=1; 14238 – undisocunted weeks of lifetime IFN administration = 14238 for every 100 patients(estimated from the survival curve of Figure 1 of Schofield's article, fit code = 10), lifetime cost per 100 patients = $2,192,652 (undiscounted) and $1,402,324 (discounted)

[b] Includes nursing time and devices for home administration (three or seven administrations per week, unit cost = $10).

[c] Lifetime value (estimated by Gompertz fit of the referenced data). The corresponding discounted values are the following. Fit 10, 9106 patient-weeks, Fit 12, 11193 patient-weeks, Fit 13, 15828 patient-weeks, Fit 14, 25532 patient-weeks; Fit 15, 27829 patient-weeks

[d] Assuming body surface area of 1 73 m^2.

[e] Determined from the actual average dose which is explicitly reported in the study.

[f] Approximate value obtained by analysis of IFN daily dose data over time presented in Figure 6a of Hellmann's article; in this study, 61 of the 126 patients who experienced disease progression continued IFN whereas the remaining 65 discontinued the treatment.

[g] Lab examinations include biochemical testing of liver function (one test every four weeks for low-dose IFN; one test every two weeks for high-dose IFN; unit cost = $40)

[h] This item includes physician's time for control and adjustment of medication (one visit every eight weeks for low-dose IFN; one visit every four weeks for high-dose IFN; unit cost = $80).

[i] Not available (the study directly provides the actual average dose of IFN).

[j] Calculated from the average daily doses which are explicitly reported by Ohnishi et al in the form of values stratified by cytogenetic response.

Cost-effectiveness ratio and sensitivity testing

The cost-effectiveness ratio was separately calculated for each of the four clinical trials (Table 4). The four values of cost per life-year gained were generally high, suggesting an unfavourable pharmacoeconomic profile for an unselected use of IFN in chronic myelogenous leukaemia.

Our first sensitivity test included a simplified meta-analysis of the effectiveness data of the four randomised trials. In this analysis, the pooled value of lifetime survival in the control groups was calculated as 4,584 discounted patient-months (average weighted by sample sizes). The pooled meta-analytic estimate of the survival gain for patients given IFN was 15.4% (95% CI: 9.7%–21.5%) in terms of relative gain, corresponding to an absolute gain of 706 months (values obtained using Simes' Method A). Application of Simes' Method B yielded essentially the same results (data not shown).

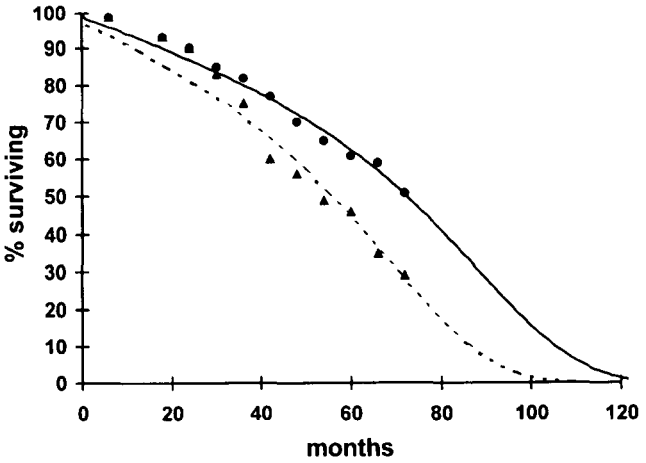

Figure 2. Italian trial. Survival curves for the IFN group (circles) and the controls (triangles) with extrapolation to infinity.

Table 4. Incremental cost-effectiveness analysis: values of the cost per life-year gained calculated from the four studies.[a]

Study	(A) Lifetime cost in the IFN group (discounted dollars per 100 patients)	(B) Lifetime cost in the control group (discounted dollars per 100 patients)	(C)[b] Incremental cost (discounted dollars per 100 patients)	(D) Incremental effectiveness (discounted patient years gained every 100 patients)	(E)[c] Cost per discounted life year gained (discounted dollars)
German trial	5,294,289	275,422[d]	5,018,867	53.7[d]	93,461
English trial	5,083,008	281,675	4,801,333	37.2	129,068
Italian trial	16,085,160	285,073	15,800,087	93.5	168,985
Japanese trial	17,532,060	269,299	17,262,761	76.2	226,545

[a] In the American trial the same data were the following: A = $1,402,324; B = $249,219, C = $1,153,105; D = 416.5 years; E = $2,769 (all values are discounted).
[b] Calculated as the difference of (A) and (B).
[c] Calculated as the ratio of (C) and (D).
[d] A pooled value of 4540 patient-months (or 19673 patient-weeks) of lifetime survival every 100 patients was first calculated for the two control groups of the German trial by computing the weighted average of the values of the busulphan (4119 patient months, n = 186) and the hydroxyurea groups (4943 patient months, n = 194); then, the value of lifetime cost for the control group ($275,422) was determined by multiplying lifetime survival (19673 patient-weeks) by weekly expenditure ($14); the incremental effectiveness of 53.7 discounted patient years (or 644 patient-months) was calculated as the difference between lifetime survival in the IFN group (5184 discounted patient months, see Table 3) minus pooled lifetime survival in the controls (4540 patient-months).

The heterogeneity among the four trials (assessed by standard techniques) was at the limit of statistical significance (data not shown).

Using this estimate of incremental effectiveness (706 months for every 100 patients), our first sensitivity analysis tested the consequences of different dosages of IFN on the cost-effectiveness ratio (Table 5). On the basis of these meta-analytic data of effectiveness, the cost-effectiveness profile of IFN was found to be poor even for relatively low dosages.

In the second sensitivity test, after introduction of the clinical results of the American trial into our meta-analysis (relative survival gain = 21.0%; absolute survival gain = 950 discounted months per 100 patients – Simes' Method A), we calculated a cost per life-year gained ranging from $56,022 for an IFN dose of 10 MU per patient per week to $204,680 for an IFN of 60 MU per patient per week.

Discussion

Our cost-effectiveness study gave a 'negative' result because our findings showed that an unselected use of IFN in chronic myeloid leukaemia has an unfavourable pharmacoeconomic ranking. While the upper limit of acceptable figures of cost per life-year gained is thought to be aroung $50,000 [see, for instance, 8–18], our data indicate that an unselected use of IFN for this clinical indication implies a cost per life-year gained considerably higher. Our sensitivity tests confirmed the poor pharmacoeconomic attractiveness of this therapy.

Table 5. First sensitivity analysis: values of cost per discounted life-year gained at different weekly dosages of IFN (values based on the results of the meta-analysis of the effectiveness data of the four trials).

Dose of IFN per patient (MU/week)	Cost per discounted life-year gained (discounted dollars)
10	72,642
20	113,309
30	149,975
40	188,641
50	227,308
60	265,974

Publication bias [25] is known to affect all kinds of medical research because 'positive' findings are more likely to be published than 'negative' ones. In the area of cost-effectiveness analysis, the publication of negative results (such as those reported in our study or, for another example, those published by Etchason et al. [11]) is particularly useful for better exploring controversial topics and can in general help to better define the range of acceptable and unacceptable values of cost per life-year gained. Recent cost-effectiveness studies on IFN have shown that the pharmacoeconomic profile of this drug is favourable for other indications such as hepatitis C [10] or melanoma [17]. In chronic myeloid leukaemia, the long-term nature of IFN administration and the modest gain in survival were certainly the main factors determining our negative pharmacoeconomic results.

One limitation of our study is that the side effects related to IFN administration [26, 27] were not incorporated in our model, mainly because it was difficult to reliably estimate their frequency and severity, and to translate them into cost estimates. This choice might have introduced a slight bias in favour of IFN (in other words, the cost effectiveness ratio considering side effects could be worse than that derived from our analysis). On the other hand, our model did not account for cases in which disease progression was delayed or the frequency reduced as a result of IFN therapy; because of this latter approximation, the cost effectiveness ratio of IFN when considering the clinical pattern and costs of disease progression in the two patient groups would tend to be better than that observed in our analysis.

Another confounding factor that might have affected our pharmacoeconomic results was that the control groups of the four trials did not use the same cytotoxic agent but rather either busulphan or hydroxyurea (Table 1). Ring and Korgh-Jensen [28] have observed that the apparent benefit obtained from the use of IFN could just as well be a disadvantage of the use of busulphan in comparison with hydroxyurea or IFN. While only a few data presently suggest that hydroxyurea is significantly more effective than busulphan, the potentially lower effectiveness of busulphan was, in our view, unlikely to explain the better overall outcome with IFN found in our analysis.

When the present study was already at an advanced stage, two articles, both addressing the issue of the cost-effectiveness of IFN in chronic myeloid leukaemia [29, 30], were published. These two studies utilised a decision-tree analysis (Markov model), wherein sophisticated simulations were carried out to predict the natural history of patients with chronic myeloid leukaemia who were given interferon or hydroxyurea. The article by Kattan et al. [29] estimated a cost-effectiveness ratio of $25,600 per life-year gained or $34,800 per quality-adjusted life-year (QALY) gained (with an IFN dose of 35 MU/m^2 per week for induction and of 15 MU/m^2 per week for maintenance), while the study by Liberato et al. [30] found a cost-effectiveness value ranging from $66,800 to $90,000 per QALY gained (with an IFN dose of 35 MU/m^2 per week). In both studies, the average utility values (introduced to quantify quality of life during IFN treatment) were around 0.75 to 0.95.

From a methodological viewpoint, there are important differences between our Gompertz study and the two Markov studies mentioned previously. While our analysis was directly based on the survival data reported in the various published trials (and on the respective experimental values of IFN dosage and IFN discontinuation), the two Markov studies evaluated a simulated cohort of patients in whom the various event probabilities were determined in part by review of the literature and in part by the judgment of a panel of experts. Regardless of these differences in the methodology, our results are in much closer agreement with those of Liberato et al. [30] than with those of Kattan et al. [29].

In a comparison between our results and those of Kattan and Liberato, it would be worthwhile to determine whether the differences were in effectiveness or costs (or both). As regards effectiveness, the survival gain estimated for patients given IFN was rather similar between our data (gain ranging from 37 to 93 discounted years per 100 patients with a meta-analytic gain of 59 discounted years per 100 patients) and those obtained by Kattan et al. (gain of 94 discounted years for every 100 patients) and by Liberato et al. (gain ranging from 104 to 129 quality-adjusted years for every 100 patients). The main differences therefore were on the side of costs. The cost data of Liberato were similar to ours. In contrast, the study of Kattan utilised lower values of cost per patient of IFN therapy, probably because some cost sources that can contribute to the increase in the overall cost (e.g., physician's time for control and adjustment of medication, cost of administration, periodical lab examinations, etc.) were not considered by these authors [31]. In summary, the difference in results between our study and those of Kattan et al. is due to the fact that the latter authors adopted a slightly higher estimate of survival gain for the IFN group and utilised a much lower monthly cost of IFN. Our study is therefore in closer agreement with the one published by Liberato et al., and both studies in fact suggest that the cost-effectiveness of an unselected long-term treatment with IFN in chronic myeloid leukaemia is poor.

In our view, since this unselected long-term use of IFN is not cost-effective, the role of this drug for this therapeutic indication should probably be limited to an initial course of one or two years only, after which non-responding patients would be switched to hydroxyurea, while those who had become cytogenetically negative would be considered candidates for continued treatment. In fact, most clinicians who treat chronic myeloid leukaemia with IFN are attempting to identify the small subgroup of patients who become cytogenetically negative and who seem to derive long-term benefit from the treatment [32, 33]. In general, research is needed to identify early predictors of response to long-term treatment with IFN in order to define a more selective use of this drug. This would significantly improve the cost-effectiveness ratio.

In November 1997, the Chronic Myeloid Leukaemia Trialists' Collaborative Group co-ordinated by R. Peto published a world-wide meta-analysis [34] of the randomised trials comparing IFN vs. chemotherapy (with busulphan or hydroxyurea) in which the clinical effectiveness of IFN was evaluated by retrieval of individual patient data from a total of seven randomised studies. The clinical data-base introduced in Peto's meta-analysis included the four trials examined in our work (Italian [2], German [3], Japanese [4], and English [1] trials) plus three trials available as preliminary results. Survival was the main clinical end-point of the meta-analysis and was assessed by non-lifetime methods. The work of Peto and associates has confirmed that IFN determines a statistically significantly better survival than chemotherapy with hydroxyurea or busulphan (five-year survival rate of 57% with IFN vs. 42% with chemotherapy). To compare our clinical results with those of the Collaborative Group, we have conducted a lifetime Gompertz analysis of the meta-analytic survival data presented by Peto et al. The results of this Gompertz analysis (mean lifetime survival per 100 patients with 5% annual discounting = 5,317 months with IFN vs. 4,376 months with chemotherapy; absolute survival gain per 100 patients = 941 months with a relative improvement of 21.5%; data from Figure 2, panel C of the article by Peto et al. [34]) are very similar to those obtained from our simplified meta-analysis (first sensitivity analysis) and, in particular, they are virtually identical to those produced by our second sensitivity analysis.

From a clinical point of view, the agreement between our analysis and the results presented by Peto et al. [34] is important because it supports the strong statistical robustness of the estimated survival gain resulting from IFN. Because our analysis examined both sides of cost and effectiveness, its pharmacoeconomic results are strengthened by this reproducible evidence on the survival benefit yielded by IFN.

*Participants

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Appendix 1

This Appendix contains the best-fit values of the parameters s, g, and c produced by our least-squares estimation for the 15 survival curves (or progression-free curves) evaluated in our study. These values are as follows:

Fit 1: $s = 0.993566$, $g = 0.970328$, $c = 1.038352$
Fit 2: $s = 0.990325$, $g = 0.994688$, $c = 1.053615$
Fit 3: $s = 0.995626$, $g = 0.988869$, $c = 1.049605$
Fit 4: $s = 0.996051$, $g = 0.985146$, $c = 1.052842$
Fit 5: $s = 0.986054$, $g = 0.977732$, $c = 1.040077$
Fit 6: $s = 0.990381$, $g = 0.992769$, $c = 1.052883$
Fit 7: $s = 0.983121$, $g = 0.999861$, $c = 1.051662$
Fit 8: $s = 0.995054$, $g = 0.973450$, $c = 1.050304$
Fit 9: $s = 0.993054$, $g = 0.983855$, $c = 1.058990$
Fit 10: $s = 0.993002$, $g = 0.999987$, $c = 1.003024$
Fit 11: $s = 0.980400$, $g = 0.999937$, $c = 1.064838$
Fit 12: $s = 0.976921$, $g = 0.709077$, $c = 1.001849$, RMSE = 14.5%; right tail = 13.2%
Fit 13: $s = 0.975121$, $g = 0.999963$, $c = 1.005883$, RMSE = 7.9%; right tail = 16.4%
Fit 14: $s = 0.992539$, $g = 0.994872$, $c = 1.047888$, RMSE = 2.3%; right tail = 22.5%
Fit 15: $s = 0.908351$, $g = 1.000000$, $c = 1.216691$, RMSE = 5.5%; right tail = 46.1%

Note that the parameters of the Gompertz function must be characterised using a large number of decimal digits [19].

Appendix 2

In some of the four trials included in our analysis, the patients treated with IFN underwent dose reductions for a variety of reasons (e.g., disease progression and drug toxicity). To obtain an estimate of the cumulative lifetime dose of IFN in these patients, our methodology determined the total number of patient-weeks of IFN administration (PWIA) and then estimated the cumulative lifetime dose by multiplying PWIA by the average weekly dose. That is:

$$\text{cumulative lifetime dose} = \text{PWIA} \times \text{average weekly dose}$$

The values of average weekly dose could differ from the target dose of the trial in cases where compliance was not 100% (e.g., because of side effects) or drug dosage was individualised. To account for these differences, a (percent) correction factor was introduced, which was calculated from the mean (or median) values of IFN dose reported by the authors of the trial (this information was explicitly reported in all four studies). Care was taken to check that the zero values of patients who discontinued IFN after disease progression were not contributed to the calculation of mean (or median) dosages reported by the trials' authors. Three methods were used to estimate the values of PWIA:

- *Method 1* was employed to handle the trials in which IFN was not discontinued upon disease progression. The value of PWIA was assumed to be equal to the lifetime survival (after the start of IFN), which was estimated in terms of AUC values using the Gompertz fit.
- *Method 2* examined the situations in which the drug was discontinued in those patients who experienced disease progression. In particular, method 2 was used for trials in which a progression-free actuarial survival curve was reported for the IFN group; in such cases, the value of PWIA was assumed to be equal to (lifetime) progression-free survival (estimated by the Gompertz fit) and its value was therefore derived from the total area under the progression-free survival curve (integral from time zero to infinity).
- *Method 3* was used for trials in which a progression-free actuarial survival curve was not reported for the IFN group, but the study explicitly reported the numbers of patients who remained under IFN treatment over time (in such cases, the decreasing number of patients taking IFN over time could result from either disease progression or simply termination of follow-up). To estimate PWIA, we constructed (by standard life-table methods) the progression-free survival curve using the following procedure: the numbers of patients who remained on IFN treatment at the subsequent time intervals were directly derived from published information, while the distribution over time of right censored patients was derived by counting the vertical tickmarks in the graph of the survival curve (German trial) or by analysing the patients' survival curves according to the method of Fine et al. [21] (English trial). In other words, the progression-free survival curve was constructed using the published numbers of patients still taking IFN and adding an appropriate number of right censored patients at each time interval. Finally, the value of PWIA was assumed to be equal to lifetime progression-free survival (which was estimated by a Gompertz fit) and its value was therefore derived from the total area under the progression-free survival curve (integral from time zero to infinity).

Methods 1, 2 and 3 share the purpose of determining the lifetime values of IFN administration, which are in fact required because in a lifetime analysis, both cost and effectiveness data are to be estimated through a lifetime perspective. Method 1 was applied for the data of the American trial, method 2 for the Italian and the Japanese trials, and method 3 for the German and English trials. In our application of method 3 to the German trial, the numbers of right-censored patients were estimated by counting the vertical tickmarks of the survival curve, and in the English trial by applying the method of Fine et al. [21]. In the German trial we found a slight inconsistency between the tickmarks of Figure 2a (which probably were too numerous) and information reported in the legend to Figure 6. To solve this discrepancy, we assigned priority to the data of Figure 6; use of the data of Figure 2a, however, yielded a virtually identical result (data not shown).

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