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Original Paper

A Retrospective Cost-effectiveness Analysis of Interferon as Adjuvant Therapy in High-risk Resected Cutaneous Melanoma

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To assess the cost per life year gained of alpha interferon (IFN) as adjuvant therapy for patients with high-risk resected melanoma, we conducted a retrospective, incremental cost-effectiveness analysis on clinical data from a previously published ECOG trial [9]. The Gompertz model was used to estimate the total lifetime values of patient-years of subjects receiving IFN in comparison with subjects given no adjuvant treatment. The ECOG trial involved 143 patients treated with high-dose IFN and 137 given no adjuvant treatment. Estimated drug expenditures were based on the assumption of a cost of $109.25 per 10 MU of IFN. Our analysis of the ECOG results showed that the adjuvant treatment of 100 subjects with high-dose IFN improved survival expectancy by 133.6 discounted life years or 308 undiscounted life years. The use of IFN (compared with no adjuvant treatment) implied an incremental cost of $16467 per discounted life year saved (95% CI of $4752–50000) or $7143 per undiscounted life year saved (95% CI of $3226–33846). Sensitivity testing, in which variations were introduced in the main factors influencing cost and effectiveness, showed that this value always remained below $50000. Our pharmacoeconomic analysis indicates that adjuvant treatment with high-dose IFN in patients with high-risk resected melanoma implies a favourable cost-effectiveness ratio. Because two other studies showed no significant survival benefit in patients receiving adjuvant IFN at lower values of total dose per patient, the controversy remains and confirmation data are needed for the ECOG trial's results. If these clinical results are confirmed, our analysis shows that the dosage of IFN given in this trial has a favourable pharmacoeconomic profile. © **1997 Elsevier Science Ltd.**

Key words: interferon, melanoma, cost-effectiveness, pharmacoeconomics

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INTRODUCTION

IN THE field of cost-effectiveness analyses [1–8], a new methodology based on the so-called lifetime approach has been employed in recent studies to evaluate health care interventions in terms of cost per life year gained [1, 3–5]. In general, incremental lifetime cost-effectiveness analyses are aimed at comparing a novel, more effective, and more costly treatment with a less effective and less expensive reference treatment using long-term survival as the primary end-point. For this purpose, the published survival curves of the two treatments are fitted to a specific mathematical model (e.g. the Gompertz function [1, 4, 5]) in order to estimate the number of patient-years totalled in each of the two patient groups and express the incremental effectiveness of the new treatment in terms of gain in life years. Life years gained are then compared with incremental costs associated with the new treatment thus allowing the estimation of the cost per life year gained.

In patients with high-risk resected melanoma, a recent large-scale randomised clinical study (ECOG trial coordinated by J.M. Kirkwood) has shown that adjuvant treatment with alpha interferon (IFN) can improve survival in comparison with no adjuvant treatment [9]. The ECOG trial [9] is the first in which a survival advantage has been demonstrated in patients receiving adjuvant IFN. Another two trials [10–12] addressed the same therapeutic problem,

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but their clinical results were more controversial and more difficult to interpret [13].

In the present study, we assessed the pharmacoeconomic profile of adjuvant treatment with IFN (according to the dosing schedule adopted by Kirkwood and associates [9]) by determining the cost per life year gained on the basis of the clinical results reported in the ECOG trial. For this purpose, we conducted an incremental lifetime cost-effectiveness analysis in which the Gompertz model was used to estimate the number of life years gained by patients receiving IFN compared with subjects given no such treatment. The clinical data of the other two controlled studies were not included in our analysis for a series of reasons that are discussed in detail below.

MATERIALS AND METHODS

Study design and perspective of the cost-effectiveness analysis

In pharmacoeconomic analysis, the particular costs and benefits vary with the perspective of the study, and the analysis can be constructed to reflect the viewpoint of either society as a whole, payers, health care providers, or patients. In the present study, costs were assessed from a social perspective 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. This is a commonly used approach [see e.g. Refs. 1, 3–8].

Cost-effectiveness and cost-utility analyses are known to differ because in the former, benefits are measured as gain in life years with no adjustment for quality of life, whereas in the latter, quality of life evaluations are incorporated into survival measurements using, for example, the so-called quality-adjusted life years (or QALYs).

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. In our cost calculations, we used a cost of IFN equal to $109.25 per 10 MU (estimate derived from the present Italian price of the drug converted into U.S.$). The cost of IFN in 1996 is around 15600 Italian Lira per MU (Exchange rate, 1533 Lira = $US1). In the U.S.A., the cost is approximately $10. The analysis compared adjuvant treatment with IFN versus no adjuvant treatment 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 an incremental benefit is the lifetime difference in life years between the two patient groups). Our work was planned as a cost-effectiveness study, and so it contained no assessments of quality of life. While it would have been preferable to carry out a cost-utility study, we decided to conduct a cost-effectiveness study for the following reasons: (1) Kirkwood's trial [9] did not perform any quality-of-life evaluation in the two patient arms and so specific data on this point were not available; (2) even though some studies [e.g. Refs 6 and 7] have utilised quality-of-life assessments made retrospectively by a panel of experts, this practice has obvious limitations because it reflects the viewpoint of physicians and not that of the patients [14].

Clinical data included in the analysis

We used the clinical data reported in the randomised clinical trial published by Kirkwood and associates (ECOG trial) [9]. This trial involved 143 patients treated with IFN and 137 who were given no adjuvant treatment. Survival was the primary end-point of the study. The last timepoint in the survival curves was at 9 years. An intention-to-treat analysis was employed to evaluate survival data.

IFN dosage and cost of IFN therapy

In the ECOG trial, IFN was given at different dosages in the induction phase versus the subsequent maintenance phase (Table 1). Patients enrolled in the treatment arm of the ECOG trial underwent dose reductions for a variety of reasons (in particular, the percentage of patients taking at least 80% of their full dose in the maintenance regimen was 67% during the induction phase and 59% during the maintenance phase). In our cost-effectiveness analysis, we assumed that patients received, on average, 60% of their scheduled full dose. This percentage value is consistent with the information reported in Kirkwood's article [9].

During the first year of the study and particularly from week 4 to week 52 (which corresponds to the period of s.c. IFN administration), there were numerous interruptions of IFN treatment caused by melanoma relapse (the relapse-free rate at 1 year was in fact around 60% in the IFN group). Assuming a homogeneous incidence of relapse over these first 12 months (as confirmed in Kirkwood's study [9], we empirically estimated that 3% of the patients enrolled in the IFN arm relapsed from week 0 to week 4 and that 37% relapsed from week 4 to week 52. To adjust the IFN administration data on the basis of treatment discontinuations caused by melanoma relapse, we employed the following procedure. Using data normalised to a group of 100 patients, the target values of IFN administration (i.e. the values assuming a 0% incidence of relapse) were quantified as 400 patient-weeks of administration of intravenous IFN and 4800 patient-weeks of administration of s.c. interferon. The area under the relapse-free curve from week 0 to week 4 (estimated by application of a trapezoidal rule) was $(100 + 97) \times 4/2 = 394$ patient-weeks, which corresponds to a 1.5% reduction in the ideal value of 400 patient-weeks of intravenous (i.v.) IFN administration. The area under the relapse-free curve from week 4 to week 52 (estimated simply by application of a trapezoidal rule) was $(97 + 60) \times 48/2 = 3768$ patient-weeks, which corresponds to a 22.5% reduction in the ideal value of 4800 patient-weeks of s.c. IFN administration. In our primary analysis (see Table 1), correction factors of 0.985 and 0.785 were, therefore, utilised in the dosage calculations of i.v. and subcutaneous (s.c.) IFN, respectively, in order to account for treatment discontinuations caused by relapses.

Lifetime cost-effectiveness analysis

Our cost-effectiveness analysis proceeded through the following phases.

(1) Estimates were obtained of the cost for treating 100 patients with either IFN or no adjuvant therapy (incremental cost = difference between these two costs). The cost data were derived exclusively from the initial year of the follow-up; in addition, because our analysis considered incremental costs, all cost sources that were thought to be similar between the two patient groups were not included in our calculations. After the first year, the follow-up costs for the two patient groups were assumed to be identical (e.g. number and length of hospitalisations, laboratory tests, expendi-

Table 1. Dosage and costs of adjuvant therapy with IFN according to the protocol of the ECOG trial [9]

	Scheduled dose per patient per day*	% of scheduled dose actually administered	Actual average dose per patient per day	No. of days of administration per week	Duration of treatment (weeks)	Total dose per patient	Correction factor to account for IFN discontinuations in relapsed patients†	"Corrected" total dose per patient	Cost of IFN‡ ($ per patient)	Cost of IFN administration ($ per patient)	Miscellaneous sources of cost (cost source, $ per patient)	Total cost per 100 patients ($)
Induction treatment	34.6 MU i.v.	60%	20.8 MU	5	4	416 MU	0.985	410 MU	4477	1600§	lab tests, ¶ 320	639 700
Maintenance treatment	17.3 MU s.c.	60%	10.4 MU	3	48	1498 MU	0.785	1176 MU	12 843	1440‖	lab tests, ¶ 440 outpatient visits, **880	1 560 300
Total						1914 MU			17 320	3040	all sources, 1640	2 200 000

* Values of the full-dose regimen (20 MU/m^2 i.v. in the induction phase, 10 MU/m^2 s.c. in the maintenance phase) assuming a body surface area of 1.73 m^2. † This factor is used to calculate the "average" dose of IFN per patient in the hypothetical population of 100 patients (see text for details). ‡ Costs calculated from the exact drug dosages assuming no waste of unused products. § Includes a total of 20 outpatient visits per patient (cost of each visit = $80; this value is close to estimates reported in the literature [3, 27]). ‖ Includes nursing time and devices for home administration (144 administrations per patient; unit cost = $10). ¶ Lab examinations include biochemical testing of liver function (8 tests in the induction phase and 11 tests in the maintenance phase; unit cost = $40). ** This item includes physician's time for control and adjustment of medication (11 outpatient visits per patient).

ture for treating drug-related side-effects, costs of terminal illness, etc.).

(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 (see below). 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 these components of the total area were determined according to the Gompertz function [1, 4, 5, 15–17] using the parameters generated by survival curve fitting (see below).

(3) The survival curve of the control group (i.e. the no adjuvant therapy group) was analysed by the same procedure described for patients given IFN. In this case, the estimation yielded the value of $AUC_{no\text{-}IFN}$.

(4) The incremental clinical benefit derived from IFN (in comparison with no treatment) was calculated as the difference of AUC_{IFN} minus $AUC_{no\text{-}IFN}$ (corrected 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 every 100 patients using IFN rather than no adjuvant treatment.

(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.

It should be noted that our hypothesis of identical costs in the two patient groups after the first year (i.e. identical lifetime costs per patient except costs of the first year) assumes that the costs incurred by patients experiencing

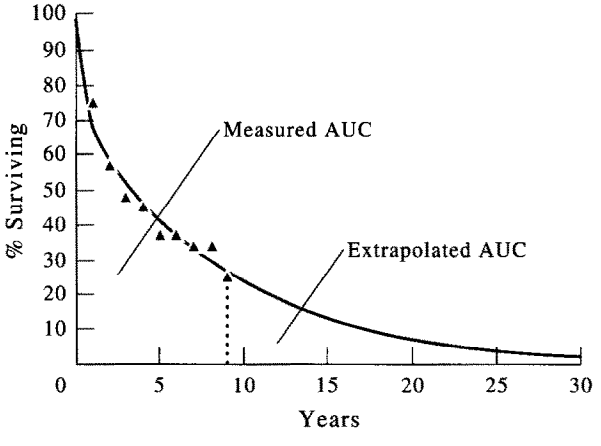

Figure 1. The least-squares fit of the Kirkwood trial's [9] survival percentages to the Gompertz function allows the determination of the whole survival curve as a mathematical function from time zero to infinity. The area under the survival curve can be split into a first component (measured AUC), which 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 (no adjuvant therapy received) of Kirkwood's study.

melanoma recurrence are part of their terminal care and that terminal care costs do not differ as a consequence of the type of terminal illness (which can be either melanoma itself or other non-cancer diseases or even another type of cancer). In other words, our model comparing 100 patients given IFN versus 100 patients given no adjuvant therapy included terminal care costs for all patients of both arms (i.e. terminal care costs for a total of 200 patients). Because terminal care costs were equal between the two groups, they could, therefore, be omitted from our estimation of incremental cost.

The reason why we chose this scenario of equal costs after the first year is that costs related to terminal care (which are likely to give the main contribution to lifetime costs following the first year) cannot be reliably predicted, and one cannot anticipate what effect there is on terminal-illness costs by the cure of melanoma (presumably achieved several years or decades before death from a different cause). Another reason for omitting terminal care costs from our incremental analysis is that cost differences between the two patient groups, if present, would have been markedly reduced by the customary practice of discounting future costs (see below). Hence, our analysis considered adjuvant therapy as the only source of (short-term) incremental costs.

Survival curve fitting and area estimations

The Gompertz function [1, 4, 5, 15–17] 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 and s, g and c are the three constants of the function.

In our curve-fitting procedures, the numerical values of the SP versus t data pairs of the survival curve were estimated from the published graph by careful measurement of the height of every step of the curve. 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 versus t data pairs while the output parameters were the best-fit values of s, g and c. When the iterative process achieved the so-called convergence, the value of the weighted sum of squared residuals (WSSR) between fitted and observed SP values produced by the final estimates of the parameters was calculated. An index of the goodness of fit [4, 5] was then determined by calculating the root mean squared error (RMSE), which is the square root of WSSR/n (where n is the number of SP versus t data pairs). Considering the statistical weight adopted (weight = 1/squared SP), the units of RMSE are essentially those of a per cent number.

Estimations of areas under the survival curve were carried out by standard numerical integration. All mathematical calculations were performed using a specific microcomputer program [17]. Our computerised procedure executes the least-squares analysis using the fitting procedures contained in a commercial microcomputer program ("PCNONLIN Version 4.0", Scientific Consulting Inc, Burnside Drive, Apex, North Carolina U.S.A.).

Discounting costs and benefits

In cost-effectiveness analyses, conventional practice [18] suggests discounting either costs or both costs and benefits using an annual discount rate of 5%. Costs derived from adjuvant therapy with IFN occurred exclusively during the first year of the treatment; considering the customary practice to discount costs at yearly intervals, there was consequently no need to discount costs because these were not presumed to occur after the first year.

In the primary analysis of our study, benefits (i.e. survival of life years) were discounted by an annual discount rate of 5% in agreement with the current standards of pharmacoeconomic analysis [18]. However, the effect of introducing no discounting of benefits was assessed in a secondary analysis.

Sensitivity analysis

Our sensitivity analysis consisted of the four following secondary analyses.

(1) First secondary analysis. An undiscounted analysis was carried out (by excluding the standard 5% annual discount rate from our estimates of clinical benefit). The cost-effectiveness ratio was recalculated using these data.

(2) Second secondary analysis. Different estimates were considered for the values of IFN dosage per patient. While, in our primary analysis, we assumed that patients received 60% of their scheduled full-dose regimen, in this secondary analysis we tested three different hypotheses in which the patients received 50%, 70% or 90% of the full-dose regimen, respectively. The cost-effectiveness ratio (using both the 5% and the 0% annual discount rate for benefits) was recalculated for each of these three hypotheses.

(3) Third secondary analysis. The survival advantage of patients given adjuvant chemotherapy versus control patients (i.e. the number of patient-years gained using adjuvant therapy) was expressed in terms of upper and lower limits of its 95% confidence interval (95% CI); the cost-effectiveness analysis was then rerun using these two extreme values of effectiveness [19].

(4) Fourth secondary analysis. In the calculation of effectiveness (gain in life years), we used exclusively the AUC values from 0 to 9 years, thus disregarding the contribution of two extrapolated tails. The cost-per life year gained was recalculated from these modified AUC data.

RESULTS

Cost of interferon treatment

Table 1 summarises the cost data used in our primary analysis. The baseline-case patient was assumed to receive a total of 416 MU of IFN in the induction phase and a total of 1498 MU in the maintenance phase (total dose per patient = 1914 MU). Hence, IFN cost was \$17320 per patient. Considering also the other sources of costs in the IFN arm (outpatient visits, cost of IFN administration, nursing, lab tests, etc.; see Table 1), the overall cost was \$22000 per patient or \$2200000 per 100 patients.

Survival curve fitting and estimation of effectiveness

In our analysis of the survival curves of the two groups, we first estimated the survival percentages from the published graph (Table 2). Then, we carried out the least-squares curve fitting, the results of which are shown in Table 3 and Figure 2. The fit was excellent for both curves

Table 2. Percentage survival in the interferon group and in the control group

Time (years)	Survival (%) Adjuvant interferon group	Control group (no adjuvant therapy)
1	84.2	74.8
2	65.3	56.9
3	55.8	48.4
4	50.5	45.1
5	47.4	36.9
6	45.1	36.9
7	45.1	33.7
8	41.1	33.7
9	41.1	25.3

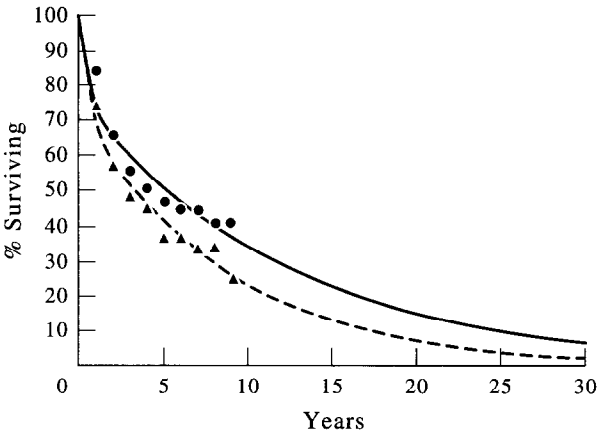

Figure 2. Survival curves for groups treated with IFN (circles) and no adjuvant treatment (triangles) with extrapolation to infinity.

(as demonstrated by the values of RMSE which were less than 2% in both fits). In the survival curve of the controls, extrapolated right tail (which is, by definition, estimated less precisely) gave a relatively small contribution to the total AUC value (34.9%, calculated from undiscounted survival data). However, the extrapolated tail was nearly half the total AUC of the curve of the treatment group (48%, calculated from undiscounted survival data), this fact being a potential drawback to a precise estimation of total AUC for these patients.

The incremental effectiveness of IFN versus no adjuvant treatment was estimated to be equal to 133.6 discounted life years or 308 undiscounted life years (both values normalised to 100 patients).

Cost-effectiveness ratio

The incremental cost per 100 subjects was simply determined as the total cost in the IFN group ($2 200 000). Using this cost estimate and the estimate of incremental effectiveness (133.6 discounted life years), the incremental cost-effectiveness ratio was calculated as $16 467 per discounted year of life gained. This value was the final result of our primary cost-effectiveness analysis.

Sensitivity analyses

In our first sensitivity analysis, the application of the 0% discount rate to life year values gave an estimate of incremental effectiveness of 308 patient-years every 100 subjects. The corresponding cost-effectiveness ratio was $7143 per undiscounted life year gained.

Table 4 summarises all results generated by our second sensitivity analysis. It can be seen that variations in the ratio of "actual dosage/scheduled dosage" did not substantially change the values of the cost per life year gained, which in fact remained below the limit of $23 000.

In the third sensitivity analysis, we first re-analysed the death risk data reported by Kirkwood and associates [9]. In patients given adjuvant IFN, the death risk was reported to be 0.67 in comparison with the controls; this risk value was significantly different from 1 ($P = 0.0115$). Using the equations published by Coplen and associates (Ref. [20]; last two equations in Coplen's appendix) and Messori and associates (Ref. [21]; equations 5 and 6), we estimated that the 95% CI for this death risk of 0.67 ranged from 0.49 to 0.91.

An approximate method [5] for redetermining this risk value using the AUC data produced by our study is to calculate the ratio of the two AUCs of the two patient groups (which is 655.7 patient-years/963.7 patient-years = 0.68, according to our undiscounted results presented in Table 3). In this sensitivity analysis, we did not change the value of 655.7 patient-years for the control group and we estimated the two extreme values of AUC for the treatment group (lowest and highest) so that these two values gave, respectively, an AUC ratio of 0.49 and 0.91 (i.e. the same values as the two extremes of the 95% CI for the death risk in Kirkwood's study [9]). The results of this calculation were the following: 721 undiscounted patients years (lowest value) and 1338 undiscounted patient-years (highest value). The corresponding incremental effectiveness was 65 and 682 undiscounted life years every 100 patients, respectively. Using these two values, the result of this sensitivity analysis

Table 3. Results of survival curve-fitting after lifetime analysis of the survival data of the two patient groups

	IFN group†	Control group† (no adjuvant IFN)	Incremental benefit‡
$AUC_{0->infinity}$ (undiscounted patient-years)*	963.7	655.7	308
$AUC_{0->last\ point}$ (undiscounted patient-years)*	501.2	426.6	74.6
$AUC_{0->infinity}$ (discounted patient-years)*	578.3	444.7	133.6
$AUC_{0->last\ point}$ (discounted patient-years)*	404.0	347.6	56.4

* Values normalised to a population of 100 subjects.

† Best-fit Gompertz parameters: IFN curve, $s = 0.924609$, $g = 0.766987$, $c = 1.007586$; no-IFN curve, $s = 0.893852$, $g = 0.733285$, $c = 1.006270$. Note: the parameters of the Gompertz function must be characterised using a large number of decimal digits [16].

‡ IFN group – control group.

Table 4. Sensitivity analysis: effect of different ratios between actual dose per patient and scheduled full dose on the cost per life year gained

Ratio of actual dose/ scheduled full dose (%)	Cost per discounted life year gained ($)	Cost per undiscounted life year gained ($)
50	14307	6206
60	16467*	7143
70	18628	8080
90	22950	9955

* Value used in our primary analysis.

was that the two extreme values for cost per undiscounted life year gained using adjuvant chemotherapy were $33846 and $3226, respectively. These two limits identify a sort of 95% CI for the value of cost per undiscounted life year saved ($7143) produced by our primary analysis.

After application of this calculation procedure to the discounted AUC values, we estimated an interval for incremental effectiveness ranging from 44 discounted life years to 463 discounted life years every 100 patients; using these latter two values, we identified a 95% CI for the cost per discounted life year gained ranging from $4752 to $50000.

In the fourth sensitivity analysis (in which the two extrapolated tails of AUC were not included in the pharmacoeconomic calculations), the cost-effectiveness ratio was estimated as $39007 per discounted life year gained (or $29491 per undiscounted life year gained).

DISCUSSION

The recent editorial published by Balch and Buzaid [13] provides an exhaustive overview of the published clinical trials evaluating the effectiveness of adjuvant IFN in patients with melanoma (ECOG trial [9], WHO trial [10, 11], and NCCTG trial [12]). The ECOG trial [9], which was the source of clinical data for our analysis, has been summarised above. In the WHO trial (which involved a total of 444 patients), the treatment arm received a low-dose regimen of IFN for a very prolonged period of time (9 MU weekly per patient for 3 years); the analysis of survival showed no significant benefit for treated patients. In the NCCTG trial (which involved a total of 262 patients), the treatment arm received high-dose IFN for a relatively short period of time (60 MU/m^2 weekly for 3 months); even in this case, the survival analysis showed no significant benefit in the IFN group.

As pointed out by Balch and Buzaid [13], the reasons why adjuvant IFN was not effective in the WHO and the NCCTG trials were probably related to the dosage schedules of IFN. Hence, it seems that very low doses of IFN for a prolonged time period or extremely high doses for a short time period are less effective than the high doses employed by Kirkwood and associates [9] for a period of 1 year.

In analysing the clinical results reported in the ECOG, the WHO and the NCCTG trials, our pharmacoeconomic study was based on the same interpretations and conclusions proposed by Balch and Buzaid [13]. Because the dosage schedules adopted in the WHO and the NCCTG trials were thought to be inadequate, these two trials were not included in our cost-effectiveness analysis, and our analysis was restricted to the only schedule of IFN improving survival at levels of statistical significance (i.e. the dosage schedule adopted by Kirkwood and associates in the ECOG trial [9]). After selecting this single trial for our analysis, our cost-effectiveness calculations weighed the improvement in survival found by Kirkwood and associates against the costs associated with the administration of high-dose IFN for 1 year and determined the consequent cost per life year gained.

One limitation of our study is that it was based on the Italian price of interferon converted into U.S. dollars. However, if we had used American prices, the total cost per patient would have been very similar (data not shown).

Our study did not contain a specific assessment to quantify costs induced by the treatment of side-effects caused by IFN, this fact being a potential weakness of our work. Kirkwood and associates [9] reported that hepatotoxicity accompanied by liver failure and death occurred in 2 patients of the IFN arm; regardless of these two fatal cases, toxicity due to IFN was mild and largely reversible on interruption or attenuation of the dosage of IFN. In this context, factors related to IFN side-effects (which could contribute to increase overall costs in the IFN arm) mainly included terminal care costs in the two fatal cases, costs related to liver function testing, and physicians' time for individualisation of IFN dosage. All of these three factors were included in our cost model, and so no further economic analysis of the consequences of IFN administration in terms of side-effects was carried out. We admit that this choice may imply a slight underestimation of the overall cost in the IFN arm.

Another limitation of our study is that, because of the lack of specific data, survival could not be weighted on the basis of the patients' quality of life [14], and a cost-utility analysis could not, therefore, be carried out. Regardless of this lack of quality-of-life data obtained within Kirkwood's trial, the instruments currently available for measuring outcomes in terms of quality of life are not yet fully standardised, and one must consequently await further methodological progress on this issue [14].

An advantage of our lifetime analysis is that the survival data reported in the ECOG trial were based on a particularly long duration of follow-up. Both survival curves had been followed until a phase in which the survival percentages had declined to relatively low values, and this fact contributed to keep the ratio between measured data and extrapolated data within an acceptable range. A comparison of the Gompertz model with alternative models of survival prediction [3, 22, 23] was beyond the scope of the present work.

Before the recent publication of some reports that applied the Gompertz technique in the area of oncology [4, 5, 26], other studies employing more traditional (non-Gompertz) models have assessed the cost-effectiveness of a wide variety of treatments including, for example, anti-hypertensive therapy versus no treatment in hypertension ($20000 per life year saved [1, 2]), haemodialysis versus no haemodialysis in renal failure ($35000 per life year saved [1, 2]), coronary bypass surgery versus medical therapy for left main coronary artery disease ($7000 per life year gained [1, 2]), interferon versus no treatment for chronic hepatitis B ($12000 per life year gained [3]), long-term therapy with beta-blockers after acute myocardial infarction ($3600–

23000 per life year gained [24]). While the upper limit of acceptable figures of cost per life year gained is generally thought to lie in the range of $50000 to $100000 (see e.g. Ref. [1]), our data on IFN indicate that the use of this drug as adjuvant therapy in patients with high-risk resected melanoma implies a cost per life year gained which is well below this cut-off value. All our sensitivity analyses, as well as the upper limit for the 95% CI of the cost per life year gained, confirmed that this cost-effectiveness ratio always remained within acceptable values.

In conclusion, our study shows that the cost effectiveness ratio of adjuvant IFN in patients with high-risk resected melanoma is favourable. In the wide area of oncological treatments, the amount of published information about cost-effectiveness ratios covers an increasing number of different issues (e.g. Refs. [4, 5, 7, 8, 25, 26]). Regardless of whether Gompertz or non-Gompertz models are utilised to determine these data, in the future cost-effectiveness techniques need to be systematically applied to the large series of commonly accepted antineoplastic treatments to determine their respective pharmacoeconomic characteristics and to produce a ranking of their economic attractiveness.

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