PERGAMON

European Journal of Cancer 37 (2001) 369–375

European Journal of Cancer

www.ejconline.com

Economic analysis of adjuvant therapy with interferon alpha-2a in stage II malignant melanoma

A. Lafuma [a,*], B. Dreno [b], M. Delaunay [c], C. Emery [a], F. Fagnani [a], K. Hieke [d], J.-J. Bonerandi [e], J.-J. Grob [e] for the French Cooperative Group on Melanoma [1]

[a] *Cemka, 43 boulevard du Maréchal Joffre, F-92340, Bourg-la-Reine, France*
[b] *CHR Hôtel-Dieu, Nantes, France*
[c] *Hôpital Pellegrin, Bordeaux, France*
[d] *Roche Pharmaceuticals, Switzerland*
[e] *Hôpital Sainte-Marguerite, Marseille, France*

Received 10 April 2000; received in revised form 28 September 2000; accepted 12 November 2000

Abstract

Using the trial demonstrating that interferonα-2a (IFNα-2a) is efficacious as adjuvant therapy in stage II melanoma, we evaluate its outcomes and economic consequences. Using rates observed in the 5-year trial and published figures, survival and Q-TWIST (Time Without Symptoms and Toxicity) were extrapolated to a 10-year and lifetime horizon. Cost analysis was performed using the trial's data, published literature and experts' opinions from the perspective of the French Sickness Funds. Patients in the IFNα-2a-group have an additional 0.26 years in life-expectancy over a 5-year time period ($P=0.046$), 0.67 years over a 10-year period and 2.59 years over a lifetime. Cost per life-year-gained was estimated at approximately €14 400 after 5 years, €6635 after 10 years and €1716 over a lifetime. Assuming that there is an improvement in disease-free survival only, cost is €26 147 per Q-TWIST. Cost-effectiveness of IFNα-2a in stage II melanoma compares favourably with estimates for widely used therapies in the oncological field. © 2001 Elsevier Science Ltd. All rights reserved.

Keywords: Cost-benefit analysis; Melanoma; Quality of life; Neoplasm recurrence; Interferon alpha-2a

1. Introduction

The incidence of malignant melanoma of the skin is increasing at a higher rate than any other cancer, with the exception of breast cancer in women. Mortality is increasing at a slower rate [1] due to earlier diagnosis (as demonstrated by a decrease in tumour thickness at the time of diagnosis [2], rather than as a result of more effective therapies. Once a patient has developed distant metastases, prognosis is poor. This has led to the testing of different adjuvant strategies either after primary tumour resection or after node dissection of regional lymph node metastases.

Several randomised controlled trials using various adjuvant therapies have been conducted. Only three, all using interferon alpha (IFNα), demonstrated a benefit in MM-patients [3–5]. A French cooperative group [5] tested low-dose IFNα-2a as an adjuvant therapy for early phase disease American Joint Committee on Cancer (AJCC) stage IIA and IIB, tumour thickness >1.5 mm, no clinically detectable lymph node involvement). IFNα-2a was administered after removal of primary melanoma lesions. Disease-free survival was significantly prolonged and there was a marked trend for a benefit in overall survival with a very low toxicity. The effect of adjuvant low-dose IFNα-2a-therapy in early

* Corresponding author. Tel.: +33-1-4091-3030; fax: +33-1-4091-3031.

E-mail address: antoine.lafuma@cemka.fr (A. Lafuma).

[1] French cooperative group on melanoma: P. de la Salmonière, D. Cupissol, B. Guillot, P. Souteyrand, B. Sassolas, J.P. Cesarini, S. Lionnet, C. Lok, C. Chastang, E. Mansat, J.P. Lacour, L Thomas, M. Beylot Barry, J.F. Truchelet, P. Chemaly, L. Machet, J. Meynadier, A. Thyss, M.F. Avril, C. Vilmer, F. Prigent, J. Chevrant Breton, S. Dalac, P. Fargeot, P. Amblard, R. Schaerrer, M. Geniaux, M. Caubel, G. Guillet, M. Baccard, J.C. Guillaume, C. Pauwels, JC. Barats, P. Wolkenstein, L. Cals, R. Laurent, C. Beylot, G. Lorette, J.P. Denoeux, I. Masson, P. Royer, M. Masson.

PII: S0959-8049(00)00411-1

phase malignant melanoma has been confirmed by preliminary results of an Austrian study [4]. However, this study is not mature enough to provide results on overall survival.

European Co-operative Oncology Group (ECOG) trial no. 1684 [3] has suggested that very high doses of IFNα-2b provide a benefit in terms of disease-free and overall survival. Preliminary results of the ECOG trial no. 1690 do not seem to confirm an impact of high-dose regimen on disease-free survival. In contrast to the Austrian and French trials, patients in the ECOG trial were at a more advanced stage of their disease and had already undergone resection of regional lymph node metastases (AJCC stage III). Severe toxicity was a limiting factor with the high-dose IFNα regimen.

The low- and high-dose studies using IFNα were not only different in terms of dosing, but also in the impact on the quality of life. They also addressed two distinct groups of malignant melanoma patients representing two successive phases in the disease history (before and after the development of clinically detectable lymph node metastases).

Despite clear clinical benefits, the adoption and use of innovative therapies depends on a favourable balance of clinical benefits versus costs to the healthcare system. Results from randomised clinical trials may underestimate the total patients' benefit because the limited follow-up period and treatment costs are not routinely included in most clinical trials. In this paper, we provide an analysis of the clinical benefits, the long-term projections, and relevant costs associated with the administration of low dose IFNα in patients who have had surgical resection of AJCC stage II primary melanoma.

2. Patients and methods

2.1. Economic analysis

There is currently no effective and well-tolerated standard for the adjuvant treatment of melanoma, and the comparator for the economic analysis is no treatment. This economic analysis adopted the standards used by the third party payer as patients are mainly fully reimbursed in France. We calculated the cost-effectiveness ratio for low-dose interferon treatment using the cost per life-year gained (LYG) as the primary parameter.

This economic analysis was performed using a previously reported, randomised controlled clinical trial [5] of low-dose IFNα-2a as adjuvant therapy after tumour resection for newly diagnosed stage II malignant melanoma. Data from the trial were re-analysed and a model was built to project costs and benefits over the total lifetime of the study cohorts. French values were used for the modelling and costing parameters.

Details of the trial have been published elsewhere [5]. In short, 489 eligible patients, ages 18 to 75 years, with a primary melanoma over 1.5 mm in Breslow thickness and no clinically detectable nodes were enrolled in the trial. They were allocated randomly to receive either IFNα-2a, 3×10^6 IU, three times per week for 18 months ($n=244$) or no medical treatment ($n=245$). Clinical examination, full blood counts and biochemical analysis were repeated every 3 months. Liver echosonography or computer-tomography (CT) scans were done every 6 months and brain scans by CT at month 18 and in yearly intervals thereafter. The date and site of first recurrence, as well as date and cause of death were recorded.

Only 10% of patients in the treatment group reported grade III or IV adverse events during the treatment period; 14% ($n=35$) of the IFNα-2a patients (the majority of which were only grade I or II) stopped therapy because of the side-effects.

The primary efficacy endpoint, analysed on the Intent to Treat opulation, was the disease-free interval which was found to be significantly longer in the treatment group ($P=0.035$, log rank test) based on a median follow-up period of 5 years. This result persisted after adjustment for age, gender and tumour thickness. Overall survival analysis showed a marked trend in favour of the IFNα-2a group ($P=0.059$). Statistical significance ($P=0.046$) was reached when the predetermined prognostic factors were taken into account using the Cox model.

The status of the patients at the end of the study period is summarised in Table 1.

2.2. Efficacy and long-term health outcomes

We assessed time to disease progression or survival during three periods. Values for period 1, ranging from 0 to 5 years after diagnosis, were based directly on the results of the clinical trial. Values for period 2 (year 6 to 10), during which relapse rates dropped, and for period 3, which ran from year 10 until death had to be estimated. Patients who entered period 3 free of relapse were considered to have been cured of malignant melanoma; when they died, the cause was assumed to be not malignant melanoma-related.

Table 1
Patient status at the end of the study period

Status	IFNα-2a + Surgery *n* (%)	Surgery alone *n* (%)
Still alive, no relapse or censored	144 (59)	124 (50)
Relapse (alive)	41 (17)	45 (18)
Dead after relapse	59 (24)	74 (30)
Dead without relapse	0 –	2 (1)
Total	244 (100)	245 (100)

IFNα-2a, interferon alpha-2a.

For each group in period 1, three actuarial survival curves [6], (cut-off at 5 years) were computed: local recurrence (including in-site metastases), distant metastases and death. For period 2, we extrapolated those curves using an annual rate for relapse of 5% for both arms because IFNα-2a was stopped at month 18 in the treated arm (5% was the observed rate during year 5, similar to the rates, 5.4 to 4.0%, published by Slingluff [7]) and an annual rate for death after relapse of 15% (based on trial data). For rates of other causes of death, we used published data on the French population [8].

For lifetime projections, we used Hakulinen's method [9] with a 1-year period, computed with using decision-tree analysis software (DATA® 3.0, Tree Age Software Inc, Williamstone MA, USA, 1996). For every month from diagnosis to year 10 (periods 1 and 2), we estimated the proportion of patients who survived, who had loco-regional relapse, who had distant metastases, and who died. For period 3, we estimated only survival. The economic analysis assessed the health outcomes and costs at the end of each of these three periods: 5 years, 10 years and lifetime.

2.3. Patient quality of life

Because different therapies produce different types and patterns of side-effects, a survival advantage can be potentially offset by deleterious effects on the patient's quality of life. To explore this issue, we used the Q-TWIST (Quality-Adjusted Time without Symptoms and Toxicity) methodology, as developed by Gelber and colleagues [10,11], to adjust the survival analysis.

This analysis compared treatment with IFNα-2a with surgery alone. Each of the months between initiation of treatment and death was categorised into three different types of health-related quality of life: TWIST (time without symptoms and toxicity), TOX (time with adverse event from IFNα-2a), and REL (time in relapse).

To adjust survival, the duration in each health state is multiplied by a utility coefficient indicating the impact on the patient's quality of life in relation to TWIST (i.e. coefficient = 1.0). TOX was assigned a utility coefficient of 0.8, and REL a 0.5 coefficient. The coefficient of 0.8 is very conservative as it assumes that patient will accept a 20% chance of death to achieve perfect health when on IFN α-2a with a side-effect.

2.4. Medical management

To estimate medical-resource consumption for standard medical management of each clinical situation we used data from the French clinical trial [4], literature and expert opinion. Data concerning IFNα-2a start date, stop date and dosage modification (temporary stop or 50% reduction) were gathered directly from the clinical trial.

Physicians from two French oncology centres that had not participated in the trial were interviewed to establish both standard follow-up protocols for patients who receive low-dose IFNα-2a, and therapy protocols administered to patients who had loco-regional and distant metastases. It was assumed that patients had a follow-up for relapse similar to that reported in a 1995 French survey [12].

Based on expert opinion, it was accepted that 75% of patients who had loco-regional metastasis had tumour resection and lymph-node resection. The remaining 25% of patients were considered to receive systemic treatments similar to that administered for distant metastases. The following three lines of treatment were chosen as a usual strategy: dacarbazine, then fotemustine, and high-dose interferon or interleukin (IL-2) last. Estimates of chemotherapy duration and success rates were based on expert opinion. Terminal care was supposed to be provided, either as standard hospitalisation or as home hospitalisation.

Using data from the clinical trial, types and rates of adverse events (defined as requiring treatment) that were possibly or certainly associated with IFNα-2a were estimated. For each type of adverse event, we assumed that the patient received the respective standard care, as defined by the experts. No costs due to malignant melanoma have been considered after year 10 for patients who did not relapse by then.

2.5. Costing

Direct costs associated with malignant melanoma were calculated for the first 10 years on a per-month basis for each clinical situation. We computed the costs for IFNα-2a administration based on the doses administered in the trial at the French list price in 1995. IFNα-2a was purchased by hospital pharmacies only in which prices are not regulated by governmental authorities.

Costs for ambulatory care were based directly on the reference values of fees negotiated by the French Health Authorities with medical associations. Fees for professional services, biological tests, and medical imaging were taken from the official lists (Nomenclature Générale des Artes Professionnels, NGAP [13], Tarifs Interministériels des Prestations Sanitaires, TIPS [14]).

Costs estimates from the national survey on [15] disease-related groups (DRG) for dermatology surgery were used to determine costs for inpatient surgery. These costs are based on medical and cost data collected from a large national sample considered by French authorities to be representative of French hospitals. Costs of systemic treatments were derived from the Assistance-Publique de Paris [16], the largest hospital group in France, which publishes the tariff per day per specialised ward every year. Tariffs for the oncology ward and for hospitalisation at home were used. The related monthly costs are shown in Table 2.

Table 2
Different clinical situations, associated type of care, resources consumed and monthly costs

Clinical situations	Type of care	Resources consumed	Monthly costs (€)
No relapse, no treatment	Disease follow-up	Oncologist visit Chest X-ray, abdomen ultrasound biological tests	17
No relapse treated by IFNα-2a	Disease follow-up	See above	17
	Specific follow-up	Extra visits and tests (liver tests, complete blood count)	43
	Cost of side-effects[a]	Extra visits and drugs according to the type and duration of the side-effects	28
	IFNα-2a	Drug costs	308
Loco-regional relapse	Relapse workup	Chest X-ray + abdomen (ultrasound) + computed tomography (CT)-scan + scintigraphy	445 (once)
	75% surgery[b]	French DRG no. 376. Other interventions on skin and soft tissues. Length of stay 7.3 days	11
	25% chemotherapy	Dacarbazine, then fotemustine interferon or IL-2 with hospitalisation (1 to 3 days for fotemustine) or home hospitalisation (for dacarbazine)	333
Distant metastases	Relapse workup	See above	
	Chemotherapy	See above	1333
Death	–		

[a] Values based on the total costs for the treatment of side-effects divided by the number of patients and by the number of months of remaining life.

[b] This estimate is based on a cost of 19 550 French francs (FF) per surgical excision, adjusted to the patients' number of months of life (months) in this condition (1 FF = US$0.16)

2.6. Sensitivity analysis

Sensitivity analyses were conducted to explore the variations of the results to plausible changes in the model's main assumptions.

- First we assumed that all patients who died from malignant melanoma received chemotherapy for 6 months or for the period between relapse and death if this was less than 6 months. As no information was available on treatments after relapse, it is possible that the number of patients receiving chemotherapy for distant metastases could have been underestimated.
- Second, costs for the treatment of relapse were varied by ±50%.
- Third, discount rates of 3 and 5% for survival and costs were applied to the relevant period of 10 years. Fourth, as the survival benefit only reached borderline statistical significance a conservative scenario assuming no survival benefit and no additional benefit in disease-free survival after the observation period ('drop-dead-assumption') was analysed (scenario 2).

3. Results

The clinical results indicated a survival benefit (0.26 years) of borderline statistical significance ($P = 0.046$) and a clearly significant benefit in terms of disease free survival ($P = 0.035$). The advantage in disease-free-survival amounted to 4.13 months per patient at the end of the observation period.

3.1. Survival benefit

The measure of incremental effectiveness was the difference in life expectancy at 5 years, at 10 years, or until death from other causes. After 5 years, a mean survival advantage of 3 months (0.26 years, 4.45 versus 4.19) was observed for patients in the IFNα-2a-arm. As described above, extrapolation of the observed data to 10 years and total lifetime resulted in a survival benefit of approximately 8 months (0.67 years) and 31 months (2.59 years), respectively (Table 3).

3.2. Quality-adjusted survival

QoL adjusted survival observed during the trial (first 5 years) is 0.286 years because of the low rate of relapse in the IFN arm (Table 4)

Table 3
Mean overall survival (years) per patient

	Directly issued from RCT 5 years (years)	Survival 1 to 10 years (years)	Survival lifetime (years)
IFNα-2a	4.45	7.87	16.87
Surgery	4.19	7.20	14.28
Difference	0.26	0.67	2.59

RCT, randomised controlled trials.

Table 4
Q-TWIST results (month) for a range of values (U_R, U_T) over 10 years

U_R	Surgery alone	U_T	Interferon-α-2a (IFN-α-2a) group	Difference in months	Difference in years
0	76.29	0	83.88	7.59	0.633
		0.5	84.38	8.09	0.674
		1	84.88	8.59	0.716
	81.35	0.5	89.18	7.83	0.653
		0.8	89.48	8.13	0.678
		0.9	89.58	8.23	0.686
		1	89.68	8.33	0.694
	86.40	1	94.48	8.08	0.673

Q-TWIST, Quality-Adjusted Time Without Symptoms and Toxicity; U_R, time in relapse; U_T, time with adverse event from IFN-α-2a.

Results are robust on assumptions concerning QoL during adverse events from IFNα-2a therapy. A change of 0.1 in the coefficient for TOX, results in a change of overall Q-TWIST of 3 days only. This is the consequence of the low rate of adverse events with this dosage of IFNα-2a and of the short duration (mean 1 month; range: 0–6 months) of the adverse events. Even with the most conservative approach with a coefficient for TOX = 0, which assumes that quality of life with toxicity is as bad as death, the interferon treatment led to a clear benefit over the surgery-alone treatment.

Results in unadjusted and Q-TWIST-adjusted survival did not differ (8.08 months), indicating that the negative impact of low-dose treatment with IFNα-2a on QoL during the treatment phase is minor.

3.3. Costs

Incremental mean costs per patient for the periods are presented in Table 5.

Distribution of costs was markedly different in the two cohorts. For the control group, the costs of relapses for the 10-year time horizon was €13 356 (92.2% of the total costs); the remaining cost of €1134 (7.8%) was attributed to follow-up. In comparison, the cost associated with the IFNα-2a strategy was €18 936. IFNα-2a intervention cost was €4913 (25.9% of the total);

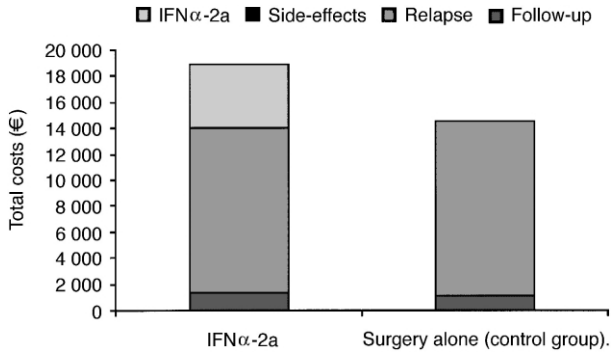

Fig. 1. Total costs of treatment per patient (10-year horizon) in €.

Table 5
Cumulated costs (€) for the different periods per patient

	First 5-year costs (€)	1- to 10-year costs (€)
IFNα-2a	11 478	18 936
Surgery	7735	14 490
Difference	3743	4446

87.2% of this figure is the cost of the drug itself (4284€), with €601 for IFNα-2a-specific follow-up cost and cost of treatment of side-effects of therapy was only €29 per patient. Costs associated with relapse in the IFNα-2a group were €12 739 (67.3% of the total costs), and the cost of follow-up was €1284 (6.8%) (Fig. 1).

The timing of costs also differed across the groups. In the treatment group, drug costs were incurred during the first 18 months. After that initial period, the major cost was for treatment of relapse, mainly for distant metastases. Follow-up costs decreased as the number of patients who had not experienced any relapse decreased.

In the control group, costs were low during the first 2 years, then increased rapidly. The largest costs were for treatment of distant metastases, followed by those for treatment of loco-regional relapse and for follow-up care.

3.4. Cost-effectiveness ratios

Without extrapolation, using the 5 years follow-up of the trial, the cost-effectiveness ratio of the treatment with IFNα-2a is €14 394 per life-year gained (LYG) and €13 086 per quality-adjusted life year (QALY). For the 10-year time horizon, the value was €6635 per LYG and €6656 per QALY; over a lifetime the value was €1716 per LYG.

3.5. Sensitivity analyses

Assuming that only the advantage in disease-free survival is a true effect of the treatment with IFNα-2a means that time is only shifted from the 'relapse' period to the 'TWIST' period (freedom from disease and no adverse events). This does not affect overall survival, however, quality-adjusted survival is improved as quality of life is better during TWIST than during relapse. The observed increase was 4.13 disease-free months per patient. Using a utility coefficient of 1 for the disease-free time and 0.5 for the time during relapse results in 2.07 additional quality-adjusted months (or 0.17 QALYs) in the IFNα-2a-arm.

The corresponding cost per month of freedom from disease was €1034 and the costs per QALY amounts to €26 147. Results of all other sensitivity analyses are presented in Table 6.

Table 6
Results of sensitivity analyses and discounting: Costs (€) per life-year gained (LYG)

Analysis	10- years cost per LYG (€)	Lifetime cost per LYG (€)
Standard analysis: Relapse rates, and death rates after relapse held constant over time (years 6 to 10)	6635	1716
Chemotherapy for 6 months prior to death	6653 (+0.3%)	1721 (+0.3%)
Cost of relapse: increase of 50%	5998 (−9.60%)	1552 (−9.60%)
Cost of relapse: decrease of 50%	7038 (+6.1%)	1821 (+6.1%)
Cost and survival discounted by 5% annually	7844 (+18.2%)	
Cost and survival discounted by 3% annually	7341 (+10.6%)	

The sensitivity analyses demonstrated that varying parameters did not influence the results substantially. Discounting is the most important parameter since additional costs are occurring at the beginning and years of life are saved in the future. When a 5% discount rate was applied, results did not dramatically change. Furthermore, cost variances of up to 50% in the treatment of relapses are likely to take into account any marginal bias and support the relevance of these data when treatment costs and strategies might differ.

4. Discussion

Low-dose IFNα-2a treatment in high-risk melanoma patients results in an increase in disease-free survival and at least a marked trend (borderline statistical significance) for an increase in overall survival provided that treatment is started before clinical involvement of regional nodes [5]. The clinical risk-benefit ratio of this regimen was shown to be favourable. The current economic analysis of low doses of IFNα-2a in stage IIA and IIB patients shows a cost-effectiveness ratio of approximately €14 400 per LYG at the end of the trial. This estimate and cost-effectiveness ratios based on extrapolations of survival and costs are lower than many accepted medical interventions. Adjusting for Quality of Life using the Q-Twist technique, supports these results. The results found in this study also compare favourably with published benchmarks [17,18] for cost-effectiveness ratios. The sensitivity analyses demonstrated that varying parameters did not influence the results substantially. Discounting is the most important parameter since additional costs are occurring at the beginning and years of life are saved in the future. When a 5% discount rate was applied, results did not dramatically change. Furthermore, cost variances of up to 50% in the treatment of relapses are likely to take into account any marginal bias and support the relevance of these data when treatment costs and strategies might differ. Therefore, estimated costs of €14 400 per life-year gained at 5 years, €6635 per life-year gained at 10 years, and €1716 per life-year gained over a lifetime are robust estimates.

Even with the most conservative assumption about the clinical efficacy, i.e. no advantage in overall survival and no benefit whatsoever after the end of the observation period of 5 years ('drop-dead-assumption', scenario

Table 7
Cost-effectiveness ratios of accepted medical technologies (adapted from Smith et al. [18]

Type of intervention	Cost per year of life saved (US$ 1992)
Liver transplantation	237 000
Cholestyramine for hypercholesterolaemia	178 000
Routine use of low-ionic contrast media	72 000–234 000
Captopril for moderate hypertension	82 600
Renal dialysis in the home	42 000–80 300
IFNα in stage III MM, (OS 10 years)	32 600 (1996 US$)
Paclitaxel versus cyclophosphamide (each plus cisplatin) in ovarian cancer	21 200[a]
Coronary artery bypass (left branch)	17 400
IFNα in stage III MM (OS 35 years)	13 700
IFNα in stage II MM (OS 10 years)	6 963 (1995 US$)
Adjuvant treatment of colorectal carcinoma with 5-fluorouracil (5-FU) + levamisole	4700*
IFNα-2a in stage II MM (OS lifetime)	1801 (1995 US$)
Anti-smoking sessions for men	1300

OS, overall survival.
[a] Year of costing not stated.

2), the results compare well with other accepted therapies in- and outside the oncological area. An increase in disease-free-survival of 4.13 months translates to costs per disease-free-month of €1034 and a cost per QALY €26 147.

A similar economic analysis of the ECOG trial no. 1684 was recently published [19]. In contrast with the French Cooperative trial, the major part of the population in the ECOG trial already had clinically detectable lymph node metastases (stage III) and the doses of IFN were much higher. The economic analysis conducted in the ECOG trial extrapolated the clinical benefits to 35 years (equal to life expectancy in their population). The main cost driver was the cost of interferon similar to our study. The estimated cost per life-year gained was US$13 700 over 35 years and US$32 600 over 10 years (1€ = US$1.07). Although it is difficult to compare costs in two different health systems, cost-effectiveness appears to be much more favourable when using low doses of IFN at an early phase of the melanoma disease than using high doses in a later phase. In contrast to the severe toxicity of high-dose IFN therapy [20], only 10% of patients treated with low-dose regimen experienced toxicity of grade 3 or higher (78% with high-dose therapy). Mean duration of toxicity was 1 month (any toxicity) versus 5.8 month (only considering grade 3 or 4) when using high-dose therapy. In the ECOG trial, as well as in the French Cooperative trial, there was no prospective assessment of quality of life, the Q-TWIST analysis presented herein shows that the clinical benefit of the low-dose treatment is not offset by its deleterious effects on the patients' quality of life.

The economic implications of a new therapeutic option have to be taken into consideration (Table 7). Cost-effectiveness ratios of low dose IFNα in stage II malignant melanoma compare favourably with many routinely used therapeutic interventions inside and outside the oncological field.

Acknowledgements

The authors thank Patrick Arveux and Marie de Zélicourt for their technical assistance. This study was supported by a grant from F. Hoffmann-La Roche Ltd.

References

1. Sober AJ, Lew RA, Koh HK, Barnhill RL. Epidemiology of cutaneous melanoma An update. *Dermatol Clin* 1991, **9**(4), 617–629.
2. Cavalieri R, Macchini V, Mostaccioli S, *et al*. Time trends in features of cutaneous melanoma at diagnosis, Central-south Italy, 1962-1991. *Ann Ist Super Sanita* 1993, **29**, 469–472.
3. Kirkwood JM, Strawderman MH, Ernstoff MS, Smith T, Borden EC, Blum RH. Interferon alfa-2b adjuvant therapy of high risk resected malignant melanoma: The Eastern Cooperative Oncology group trial EST 1684. *J Clin Oncol* 1996, **14**(1), 7–17.
4. Pehamberger H, Soyer HP, Steiner A, *et al*. Adjuvant interferon alfa-2a treatment in resected primary stage II cutaneous melanoma. Austrian Malignant Melanoma Cooperative Group. *J Clin Oncol* 1998, **16**(4), 1425–1429.
5. Grob JJ, Dreno B, de la Salmoniere P, *et al*. Randomised trial of interferon alpha-2a as adjuvant therapy in resected primary melanoma thicker than 1.5 mm without clinically detectable node metastases. French Cooperative Group on Melanoma. *Lancet* 1998, **351**, 1905–1910.
6. Haycock KA, Roth J, Gagnon J. *Statview Statistical Software 1992*. Berkeley, CA, Abacus Concept Inc, 1992.
7. Slingluff Jr CL, Dodge Jr RK, Stanley WE, Seigler HF. The annual risk of melanoma progression. Implications for the concept of cure. *Cancer* 1992, **70**, 1917–1927.
8. Institut National de la Statistique et des Etudes Economiques (France). *Annuaire Statistique de la France*. Paris, The Institut, 1996.
9. Hakulinen T, Abeywickrama. A computer program package for relative survival analysis. *Comput Methods Programs Biomed* 1985, **19**, 197–207.
10. Gelber RD, Gelman RS, Goldhirsch A. A quality-of-life-oriented endpoint for comparing therapies. *Biometrics* 1989, **45**(3), 781–795.
11. Gelber RD, Goldhirsch A, Cavalli F. Quality-of-life-adjusted evaluation of adjuvant therapies for operable breast cancer. *Ann Intern Med* 1991, **114**, 621–628.
12. Agence Nationale pour le Développement de l'Evaluation Médicale (France). *Conférence de Consensus: Suivi des Patients Opérés d'un Mélanome de Stade 1*. Paris, The Agency, 1995.
13. Union des Caisses Nationales de Sécurité Sociale (France). *Nomenclature Générale des Actes Professionnels*. Paris, The Union, 1996.
14. Union des Caisses Nationales de Sécurité Sociale (France). *Tarif Interministériel des Prestations Sanitaires*. Paris, The Union, 1996.
15. Mission, P.M.S.I. du Ministère de la Santé (France). *Echelle Nationale des Coûts Relatifs*. Paris, The Union, 1995.
16. Ville de Paris (France). *Tarif des Services Hospitaliers de l'Assistance-Publique de Paris*. Paris, Bulletin Officiel de la Ville de Paris, 1995.
17. Laupacis A, Feeny D, Detsky AS, Tugwell PX. How attractive does a new technology have to be to warrant adoption and utilization Tentative guidelines for using clinical and economic evaluations? *Can Med Assoc J* 1992, **146**, 473–481.
18. Smith TJ, Hillner BE. The efficacy and cost-effectiveness of adjuvant therapy of early breast cancer in premenopausal women. *J Clin Oncol* 1993, **11**(4), 771–776.
19. Hillner BE, Kirkwood JM, Atkins MB, Johnson ER, Smith TJ. Economic analysis of adjuvant Interferon Alfa-2b in high risk melanoma based on projections from Eastern Cooperative Oncology Group 1684. *J Clin Oncol* 1997, **15**, 2351–2358.
20. Cole BF, Gelber RD, Kirkwood JM, Goldhirsch A, Barylak E, Borden E. Quality of life-adjusted survival analysis of interferon alfa-2b adjuvant treatment of high-risk resected cutaneous melanoma: an Eastern Cooperative Oncology Group Study. *J Clin Oncol* 1996, **14**, 2666–2673.