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Original Paper

Cost-effectiveness Assessment of Interferon Alfa-2b as Adjuvant Therapy of High-risk Resected Cutaneous Melanoma

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The use of interferon alfa-2b (IFN-α2b) as adjuvant therapy of high-risk resected cutaneous melanoma was recently found to significantly improve relapse-free and overall survival in the Eastern Cooperative Oncology Group trial 1684 (E1684). However, treatment toxicities and costs may limit its widespread use. A cost-effectiveness and cost-utility analysis of this therapy was conducted using a hypothetical cohort of patients as if they had entered E1684. Survival and recurrence rates were calculated at 7 and 35 years for typical 50-year-old melanoma patients based on the clinical results of E1684 and natural history databases. Costs included all treatment-related costs (i.e. drug acquisition and administration, monitoring and treatment-related toxicity) and the costs of treating recurrences. Estimated utility values were assigned based on data from other oncology trials. The model predicted that IFN-α2b provided an extra 0.52 years of life compared with observation at 7 years; however, at 35 years, the survival benefit of IFN-α2b increased almost 4-fold to nearly 2 years. At 7 years, the cost per year of life gained was U.S. $32 600 and the cost per quality-adjusted life-year (QALY) gained was U.S. $43 200. At 35 years, these costs decreased to U.S. $13 700 and $15 200, respectively. These costs are comparable with those of other well-established medical interventions. Although these results require confirmation in a prospective study, it appears that the use of high-dose IFN-α2b for patients with high-risk melanoma is cost-effective. © **1998 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

TRADITIONALLY, PATIENTS with malignant melanoma that had not spread beyond regional lymph nodes were managed surgically, with resection of the primary tumour and, depending on prognostic factors, removal of regional nodal basins. Recently, however, adjuvant therapy with interferon alfa-2b (IFN-α2b, Schering-Plough) produced a significant impact on relapse-free and overall survival in patients with high-risk resected cutaneous melanoma [1]. The Eastern Cooperative Oncology Group (ECOG) trial 1684 (E1684) evaluated 287 melanoma patients who received either IFN-α2b at maximally tolerated doses for 1 year or observation. After a median follow-up period of 6.9 years, patients receiving IFN-α2b had a longer disease-free survival (1.7 versus 1 year) and overall survival (3.8 versus 2.8 years) compared with those in the observation group.

However, it is important to balance the benefits of this therapy with its 1-year duration, toxicity and treatment costs. In an effort to quantify the long-term benefits and cost-effectiveness of IFN-α2b, we performed an economic analysis combining prospectively collected data on IFN dosage, recurrence and survival with secondary data on long-term melanoma recurrence risks. The comparative regimen for this analysis was no therapy, as IFN-α2b is the only adjuvant therapy proven effective in high-risk primary cutaneous melanoma patients. The calculation of incremental cost-effectiveness ratios is expected to aid patients, providers and healthcare payers in making decisions about the financial implications of adjuvant IFN-α2b therapy. This work has been previously reported [2], but is reviewed again here.

STUDY DESIGN

A hypothetical cohort of 50-year-old, newly diagnosed, resectable, primary cutaneous melanoma patients was evaluated in the analysis based on projections from E1684 study

data, including clinical results and IFN dosage. In E1684, patients with histologically proven primary cutaneous melanoma without prior systemic adjuvant therapy and without evidence of distant metastatic disease were randomised to receive either IFN-α2b or observation. Patients assigned to the IFN group received IFN-α2b 20 MU/m^2 intravenously (i.v.) 5 days per week for 4 weeks, followed by IFN-α2b 10 MU/m^2 subcutaneously (s.c.) three times weekly for 48 weeks [1]. Because the median duration of follow-up in E1684 was 6.9 years, the long-term effects of therapy were projected to full-life expectancy of 85 years, calculated as 35 years beyond the median age of melanoma patients (i.e. 50 years).

Recurrence and survival rate estimates

Hazard rates (i.e. risk of recurrence per year) for years 1 and 2 were derived from actual E1684 patient data. For years 3–5, the observed hazard rates in the trial were used and beyond year 5, data were derived from the University of Alabama Birmingham/Sydney international database [3]. Recurrence-free survival and hazard rates from this database at 5 years and beyond for patients with no previous recurrence are summarised in Table 1. The Duke Registry [4] was used to estimate hazard rates for patients who had been treated with surgery for local recurrence and who remained disease free 5 years later. The registry includes 1680 patients with greater than 5 years of follow-up and 413 patients with more than 10 years of follow-up. In these patients, the subsequent risk of systemic recurrence was estimated to be 4 to 7% per year up to 12 years after local recurrence. The long-term survival rates of the cohort also were adjusted to incorporate non-melanoma-related deaths (e.g. diabetes, hypertension, stroke) based on standard age-adjusted mortality beginning at age 55. The model assumed that the average survival from relapse to death was constant over time.

Cost estimates

Only direct medical costs, expressed in U.S. dollars ($; exchange rate: $1.00 = £0.592), were included in this analysis and they were divided into two major categories: (1) adjuvant treatment costs, which included the costs of drug therapy and treatment of toxicity; and (2) the costs of recurrence. IFN-α2b costs were based on an average wholesale unit cost of $10.98/MU and were calculated by multiplying the median dosage administered in E1684 (induction = 370 MU/m^2; maintenance = 678 MU/m^2) by the median body surface area (1.9 m^2) of patients in the trial. All other treatment-associated costs, including professional, nursing and laboratory costs, of scheduled visits and those required by treatment toxicity were estimated based on clinical experience. Administration and monitoring costs were estimated to be $4 000 during the initial 4-week induction period and $200 per month during the maintenance period. The model assumed that there were no differences in the costs of primary surgery, staging, or physician monitoring between IFN-α2b-treated patients and controls.

Estimating treatment costs of recurrent melanoma was difficult since there is broad variation among expert estimates in both the U.S. and Europe. In addition, no published sources of recurrent melanoma treatment costs were identified. Therefore, a consensus of experts estimated $5 000 per month to treat recurrences, with an increase to $10 000 for the terminal month. It was assumed that patients in the IFN-α2b and observation groups incurred similar costs for the treatment of recurrence and that average survival from relapse to death was constant regardless of when relapse occurred.

Utility estimates

IFN toxicity resulted in dose delays and/or dose reductions in 37% of E1684 patients during induction therapy and in 36% during maintenance therapy [1]. Because quality-of-life data were not collected prospectively in E1684, the economic analysis was performed with and without assigned quality-of-life adjustments. Utilities reflect a patient's preference for a specific level of functional and psychological health. Utility scores take into account improved outcomes as well as toxicities associated with treatment and are generally measured on a numerical scale (0–1) where 0 represents death and 1 represents the best possible outcome. Utility values were assigned based on prior experience in cancer patients (Table 2). Patients with cancer who are confined to home but who are independent in daily activities have reported utility values of 0.73 and those with recurrent, metastatic disease have reported utility values of 0.54 [5, 6].

The model's primary endpoints were overall survival and cost per life-year gained. Secondary endpoints included disease-free survival, quality-adjusted survival and cost per quality-adjusted life-year (QALY) gained.

COST-EFFECTIVENESS

Survival and cost of care

The projected survival and relapse-free survival at 5, 7 and 35 years based on this model are shown in Table 3. The predicted values from the 5-year analysis validated the accuracy of the economic model since no differences in outcome parameters were observed from the original study data. The average patient gained almost 2 years in overall survival with IFN-α2b treatment (8.96 versus 7.06 years) [2]. The absolute difference between treatment groups narrows over time (9.3%

Table 1. Natural history of stage III melanoma at 5 years and beyond

Year	Recurrence-free survival (%)
5	50
7	38.5
10	32.9
15	29.3
Years	**Hazard rate* (%)**
5, 6	15
7–9	5.4
10–14	2.5

*Risk of recurrence per year.

Table 2. Utility assignments for patient outcomes

Outcome	Utility value
Disease free, no treatment	1.0
Disease free, maintenance IFN-α2b	0.8
Disease free, induction IFN-α2b	0.7
Alive with recurrence	0.5

Table 3. Survival and relapse-free survival

	IFN-α2b (%)	Observation (%)	Difference (%)
Survival			
5-year			
Model	43	34	9
E1684	46	37	9
7-year	35.8	26.5	9.3
	(3.99 years)	(3.47 years)	(0.52 years)
35-year*	5.4	4.0	1.4
	(8.96 years)	(7.06 years)	(1.90 years)
Relapse-free survival			
5-year			
Model	36.8	25.8	11
E1684	37	26	11
7-year	32.8	23.1	9.7
35-year*	5.8	4.3	1.5

*Projected.

at 7 years and 1.4% at 35 years) due to the increased impact of mortality from other causes with long-term follow-up.

When survival was adjusted for quality of life, the difference between treatment groups was slightly less than that seen for overall survival. At 7 years, patients receiving IFN-α2b had 3.66 QALYs compared with 3.20 QALYs for those in the observation group [2]. When the life expectancy of patients was projected to 35 years, patients receiving IFN-α2b had 6.06 QALYs compared with 4.87 QALYs for those in the observation group, a difference of 1.2 years.

The costs of care are shown in Table 4. The costs of IFN-α2b treatment exceeded the cost savings from avoiding treatment for melanoma recurrence by $15 076 and $18 123 after 7 and 35 years, respectively [2]. At 7 years, the cost per year of survival gained for IFN-α2b was $32 600 and the cost per QALY was $43 200. However, at the projected life expectancy of 35 years, these costs were reduced to $13 700 and $15 200, respectively.

Sensitivity analyses

Sensitivity analyses were performed to determine whether changes in the initial assumptions regarding costs of recurrence and utility assignments for quality of life would affect the outcome of the analysis [2]. Cost-effectiveness ratios were recalculated after ignoring the costs of recurrent disease. Under this assumption, the cost per year of life saved with IFN-α2b treatment was $61 700 and the cost per QALY was $81 600 at 7 years. At 35 years, these costs were reduced to $21 600 and $23 900, respectively. An analysis also was conducted assuming that quality of life associated with IFN-α2b therapy and melanoma recurrence is equal to death. Under these assumptions, treatment with IFN-α2b was associated with a decrease of 0.07 QALYs compared with observation at 7 years. However, when the analysis was carried out to 35 years, IFN-α2b produced an increase of 0.76 QALYs compared with observation, corresponding to a cost of $23 260 per QALY. Therefore, even at extremes of quality of life, IFN-α2b has a pronounced effect on projected long-term survival [2].

Table 4. Costs of care by treatment group and cost-effectiveness ratios

Costs (U.S. $)	IFN-α2b	Observation	Difference
IFN therapy	28 636	0	28 636
Total cost of care*			
7-year	91 656	76 580	15 076
35-year†	105 479	87 356	18 123
Cost effectiveness ratios (U.S. $)			
Cost per life-year saved			
7-year	32 600		
35-year†	13 700		
Cost per quality-adjusted life-year saved			
7-year	43 200		
35-year†	15 200		

*Includes IFN therapy and treatment costs of recurrent disease.
†Projected.

Table 5. Cost-effectiveness ratios based on 1997 average prices for IFN-α2b in the three largest European markets

Market	IFN-α2b price per million units ($)	Cost-effectiveness ratio at 35 years ($)	Cost-effectiveness ratio with no recurrence costs ($)
France	8.32	8 500	16 370
Germany	11.46	14 685	22 600
U.K.	8.59	9 040	16 900

The baseline analysis was also calculated using the 1997 average prices for IFN-α2b in the three largest European markets; all other cost elements were unchanged. The results shown in Table 5 indicate little variation in the incremental cost-effectiveness ratios. When recurrence costs are excluded, the incremental cost-effectiveness ratios are higher, but avoid having to protect total treatment costs.

CONCLUSIONS

The E1684 trial demonstrated that the use of high-dose IFN-α2b as adjuvant treatment in patients with high-risk resected cutaneous melanoma is associated with significant improvements in relapse-free survival and overall survival compared with observation alone. However, despite these improved outcomes, the associated toxicities, their effects on quality of life and the high cost of treatment are cause for concern among patients and physicians considering the use of this regimen. A previous quality-of-life analysis of E1684 using the quality time without symptoms of disease and toxicity of treatment (Q-TWiST) methodology found that patients receiving IFN-α2b had more quality-adjusted time than patients who received no treatment [7]. The current economic analysis demonstrates that, under most scenarios and time frames, adjuvant IFN-α2b leads to substantial benefits in survival and quality-adjusted survival, particularly when benefits are projected over a lifetime. At 7 years, the difference in survival duration between the treatment groups was approximately 0.5 years in favour of IFN-α2b treatment. However, taking a 35-year perspective, the survival benefit of IFN-α2b increased almost 4-fold to nearly 2 years. Adjusting for quality of life, the survival benefit remained significant, with 1.2 QALYs for patients treated with IFN-α2b adjuvant therapy.

The incremental cost associated with the survival benefit of IFN-α2b is similar to or lower than that reported for other

widely used medical interventions. Projected over a lifetime, the incremental cost per life-year or QALY from IFN-α2b therapy was less than $16 000. In comparison, we previously demonstrated that the use of adjuvant chemotherapy in women with node-negative breast cancer resulted in a cost of $15 400 to $18 800 per QALY gained [8]. Haemodialysis for end-stage renal disease costs approximately $15 000 to $25 000 per life-year depending on the location of dialysis (i.e. home or facility, respectively) [9] and similar costs are documented for the treatment of hypertension [10]. Considering only the 7-year period based on the median follow-up of E1684, the cost-utility ratio of IFN-α2b was approximately $43 000. This remains lower than costs per life-year saved associated with bone marrow transplantation or chemotherapy for acute nonlymphocytic leukaemia ($62 500 or $64 000, respectively) [11]. When examined in the context of other common medical interventions, particularly oncology interventions, the use of adjuvant IFN-α2b in high-risk resected cutaneous melanoma patients appears to be a rational healthcare expenditure.

Cost of recurrent disease had the greatest impact on the cost-effectiveness ratios. Because accurate estimates of treatment costs for recurrent melanoma were not identified, an expert panel was consulted to provide these costs. However, when recurrence costs were excluded in a sensitivity analysis, the lifetime incremental cost of IFN-α2b remained within the range of other medical interventions at $21 600 per life-year gained. Similarly, when the quality of life associated with IFN-α2b treatment or recurrence was considered to be equal to death, the cost per QALY was approximately $24 000. Future studies should include quality-of-life parameters as well as measures of deferred costs of care associated with adjuvant IFN-α2b therapy to prospectively measure the cost-effectiveness and cost-utility of this regimen.

Adjuvant IFN-α2b therapy for high-risk resected cutaneous melanoma effectively prolongs relapse-free and overall survival [1] even when adjusted for quality-of-life utilities. The treatment also has an incremental cost-effectiveness ratio at 7 years similar to other medical interventions, including those for malignant disease. In addition, if response durability observed to date with adjuvant IFN therapy endures and reflects cure, the cost-effectiveness ratio will continue to decline over time.

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