Pergamon

European Journal of Cancer, Vol. 33, No. 9, pp. 1345–1346, 1997

Printed in Great Britain
0959-8049/97 $17.00+0.00

PII: S0959-8049(97)00184-6

Editorial

Economic Analyses of Benefit from Interferon-Alpha 2B in High-Risk Melanoma: Trade-offs between Completeness, Simplicity and Clarity

B.E. Hillner[1] and J.M. Kirkwood[2]

[1]Division of General Internal Medicine, Medical College of Virginia, Virginia Commonwealth University Box 980170, Richmond, VA 23298-0170, U.S.A.; and [2]Department of Medicine, University of Pittsburgh Medical Center, 200 Lothrop Street, Pittsburgh, PA 15213-2582, U.S.A.

MELANOMA HAS been one of the most provocative and, at the same time, elusive human neoplasms: it has shown responsiveness in the range of 20% objective remissions with a multitude of immunobiological interventions ranging from the crude microbial immunostimulants and, more recently, recombinant DNA-produced cytokines. It has also defied curative systemic medical intervention efforts with chemotherapy, radiation therapy and, until recently, immunobiological agents. The hope for the future is that high technology of immunology will bring therapies that are specific (and therefore nontoxic), as well as effective (and therefore low cost).

A large randomised controlled multicentre trial of the Eastern Cooperative Oncology Group (ECOG 1684) has broken the 'losing streak' for melanoma adjuvant therapy, in general, and immunobiological therapy, in particular. The E1684 trial was the first to show a substantial survival advantage, employing high-dose interferon (IFN) alpha-2b (Intron A, Schering-Plough, Inc., Kenilworth, New Jersey, U.S.A.) administered intravenously daily × 5/week for one month, then thrice weekly for 11 months [1]. The E1684 trial was unusually mature at the time of first publication, with a median follow-up of 6.9 years. The impact of treatment on relapse rate was most pronounced early in the treatment interval, and was most beneficial among node-positive strata which comprised 90% of patients accrued to the trial.

Unfortunately, the IFN treatment regimen which achieved these gains is associated with several real and perceived barriers to its more widespread use. These include the well-described constitutional symptoms, potential haematological and hepatic toxicities, initial requirement of intravenous administration (generally in hospital or office) followed by self-administration of the agent for 11 months, and the cost of the drug. A full one-year course of therapy costs approximately $30 000, principally due to the cost of the therapeutic agent itself. This situation is representative of an increasingly frequent scenario where a new intervention is convincingly shown to be beneficial but its costs are perceived to 'break the budget'.

Correspondence to J.M. Kirkwood.
Received 1 Apr. 1997; accepted 7 Apr. 1997.

Prioritising the allocation of limited resources is a common challenge independent of the structure of health care in a given nation. The history of cost-effectiveness analysis in medicine, in general, and oncology, in particular, has involved the development of models using hypothetical cohorts of patients in which treatment efficacy and toxicity are based on an abstraction of the relevant clinical trial data, ideally from a meta-analysis [2]. An alternative and increasingly common approach is to perform an economic analysis of a single trial, ideally the largest and most definitive trial assessing an intervention to date. Such assessment of a single trial can be done either prospectively or retrospectively using either the primary trial data or an abstraction from the scientific report. In addition, several authoritative sources have recently made recommendations on the reporting of cost-effectiveness studies in medicine [3,4]. In this issue, Messori and colleagues (pp. 1373–1379) report an assessment of the cost-effectiveness of IFN based on data abstracted from the published data of the trial E1684. We have independently completed an assessment of data obtained from the same trial (Hillner and associates, in press). It is a compliment to the clarity of the initial presentation and the publisher's willingness to provide sufficient journal space that such an abstraction was possible in the first place.

As reported by Messori, a Gompertz survival model was constructed for 9 years from the specific datapoints abstracted from the publication when available, or the point estimates from graphs of survival and recurrence data of E1684. IFN dosing was based on a reasonable assumption of 60% of scheduled dose, a homogeneous rate-of-relapse for the first year, and a correction or 'fudge factor' for dose reduction. Whether and how costs for regionally-recurrent or metastatic disease within the first year were handled is not clear. It appears that they were excluded, implying that the costs analysed were only those incurred with delivering adjuvant therapy. Beyond the first year, all patients were assumed to incur the same costs for metastatic or terminal disease. However, the absence of such costs in a cured fraction of the population needs to be considered. Exactly how the

Table 1. Comparison between current and future assessments of adjuvant melanoma therapies

	Messori and associates	Hillner and associates	Ideal
Data sources	Abstracted from report	Primary data	Primary data
Treatment dosage	Estimated at 60% of intent	Based on median dose delivered	Primary individualised dosage
Dose schedule within year 1	Assigned and fixed	Estimated, if recurrence free	Actual dose and schedule delivered
Costs for metastatic disease	Excluded	Included	Included
Discounting	Included	Included	Included
Time horizon	Lifetime	Lifetime	Lifetime
Late recurrence risk	Gompertz coefficient	Natural history databases	?
Confidence intervals	Efficacy	None, sensitivity analysis	Cost and efficacy
Utilities or quality of life	None	Assigned	Prospectively collected
Drug costs	Average wholesale price	Average wholesale price	Purchase price

Gompertz function projects survival beyond the lead datapoint of 9 years is unclear, i.e. the slope of subsequent survival curve. The model concluded that the IFN patients had an average projected lifetime survival of 9.6 years, which would be an increase of 3.1 years per patient. When future benefits are discounted by 5% per year, the increase in life expectancy was 1.3 years. Given an average projected adjuvant treatment cost of $22 000 per patient, the incremental cost-effectiveness ratio was $16 467. Of the total survival benefit, 35–48% in each cohort occurred beyond year nine.

Although it is unclear whether the authors recognise it as such, the analyses' main results when reported as a ratio of survivals (undiscounted)—Control/IFN 6.56 years/9.64 years = 0.68—confirms that the model is an accurate projection of the actual trial result (hazard rate for death = 0.67). The most clever part of this analysis was in their projection of the confidence interval around their cost-effectiveness estimate. Using equations that we were unaware of, the confidence intervals around the death risk projection were made to provide a high and low point for survival and cost-effectiveness projections. As shown in Figure 1, when efficacy and incremental cost-effectiveness are plotted, the authors could establish a left and right horizontal line for efficacy. However, since no cost ranges were used, a vertical top and bottom line to complete a potential cost-effectiveness rectangle could not be generated [5] (see Figure 1). Still, policy-makers generally find reporting cost-effectiveness analysis as a range more useful than a single-point estimate. The differences in the approach we took are notable for their greater completeness, but do not necessarily alter the conclusion of the analysis and likely took much longer to complete. These points are summarised in Table 1. What is notable is the similarity of the primary conclusions. Our model's projected lifetime IFN benefit is 2.2 years and incremental cost-effectiveness ratio is $15 380 per quality adjusted year.

We believe a compelling case can be made that adjuvant high-dose IFN should be the worldwide standard of care in nations whose economies routinely provide adjuvant therapies for other cancers and conditions common to developed countries. Politically, the agenda is clear—that such assessments will be needed to guide reluctant healthcare systems. Scientifically of importance is how limitations in this model are representative of current economic assessments and how future multi-institutional trials should collect their data. Investigators who do 'secondary' data analysis often forget that primary data collection is expensive. The increasing interest in quality-of-life assessments has increased the costs per patient enrolled in trials. For most trials, this is likely to

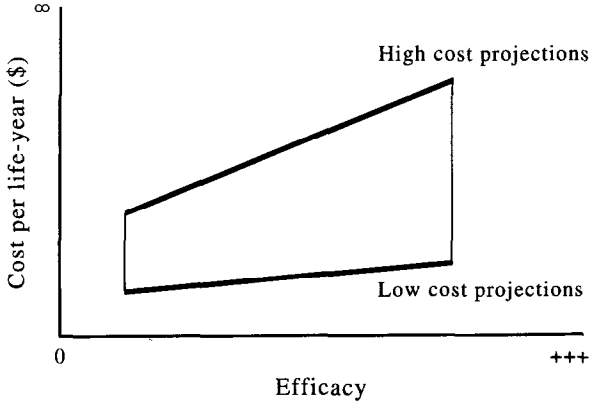

Figure 1. Cost projections against efficacy.

be a sound investment; however, sometimes it is overkill or tangential to the primary objective. The same can be said for economic analyses in parallel with trials. As outlined in greater detail elsewhere [6], studies where this is appropriate include treatments that differ substantially in financial costs, long-term quality-of-life, or short-term morbidity and mortality. In addition, future comparisons between economic assessments are needed when simple models such as that reported here by Messori and associates are compared to more complex ones. At least for IFN in high-risk melanoma, the cost-effectiveness projections are so alike that this consistency lends credence to their outcome.

1. Kirkwood JM, Strawderman MH, Ernstoff MS, Smith TJ, Borden EC, Blum RH. Interferon alfa-2b adjuvant therapy of high-risk resected cutaneous melanoma: the Eastern Cooperative Oncology Group Trial EST 1684 [see comments]. *J Clin Oncol* 1996, **14**, 7–17.
2. Smith TJ, Hillner BE, Desch CE. Efficacy and cost-effectiveness of cancer treatment: rational allocation of resources based on decision analysis. *J Natl Cancer Inst* 1993, **85**, 1460–1474.
3. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. *BMJ* 1996, **313**, 275–283.
4. *Cost-Effectiveness in Health and Medicine*. New York, Oxford University Press, 1996.
5. O'Brien BJ, Drummond MF, Labelle RJ, Willan A. In search of power and significance: issues in the design and analysis of stochastic cost effectiveness studies in health care. *Med Care* 1994, **32**, 150–163.
6. Hillner BE. Potential evaluation of the incremental cost-effectiveness of paclitaxel in advanced non-small-cell lung cancer (Eastern Cooperative Oncology Group 5592). *Monogr Natl Cancer Inst* 1995, 65–67.