Post hoc economic analysis of temozolomide versus dacarbazine in the treatment of advanced metastatic melanoma

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Two drug therapies for the palliative care of patients with advanced metastatic malignant melanoma were examined. The two therapies were intravenous single-agent dacarbazine (DTIC) and oral temozolomide (TEM). DTIC was administered intravenously once a day for 5 days, at a starting dose of 250 mg/m2/day, and repeated every 21 days. TEM was administered orally once a day for 5 days, at a starting dose of 200 mg/m2/day, and repeated every 28 days.

Type of intervention
Palliative care (chemotherapy).

Economic study type
Cost-effectiveness analysis.

Study population
Details of the study population were obtained from the paper reporting the original effectiveness results (see Other Publications of Related Interest). The study population comprised patients with histologically confirmed, surgically incurable advanced metastatic malignant melanoma, with at least one measurable site, who had not been treated for metastatic disease. The patients were at least 18 years old, with measurable disease, adequate performance status (World Health Organisation status 0, 1 or 2) and specific renal, hepatic, and bone marrow functions. Patients with relapsing disease requiring systemic chemotherapy after isolated limb perfusion (but not with DTIC) were eligible for inclusion. A single regimen of adjuvant biologic therapy was also acceptable. Any prior treatment had to have been completed at least 4 weeks before administering one of the study drugs.

Patients were excluded if they had received prior treatment for metastatic disease other than local radiation therapy, had disorders which could interfere with the oral intake of the study drug, or had infections requiring systemic antibiotic therapy. They were also excluded if they were pregnant or nursing patients, or had other indications of poor medical risk.

Setting
The setting of the study was presumed to be the hospital. The economic study was carried out in 34 centres worldwide.

Dates to which data relate
The effectiveness evidence and resource use data were gathered from 16 July 1995 to 25 February 1997. The price year was 1999.

Source of effectiveness data
The effectiveness evidence was derived from a single study (see Other Publications of Related Interest) and the authors' assumptions.
Link between effectiveness and cost data
The costing was undertaken largely prospectively on the same patient sample as that used in the effectiveness analysis.

Study sample
Power calculations were performed in the planning phase to determine the sample size. A total sample of 260 patients was required to detect a minimum median survival increase of 3 months (6 months for DTIC versus 9 months with TEM), with an 80% power and an overall 5% level of significance (two-sided). The method used to select the sample was not reported. Overall, 305 patients were included in the sample. There were 149 subjects in the DTIC group and 156 in the TEM group. The median age in the DTIC group was 58.8 years (range: 21 - 82) and 54% of the patients were male. The median age in the TEM group was 58.5 years (range: 24 - 88) and 63% were male. Ten patients assigned to the TEM group, and 8 patients in the DTIC group, were found to be ineligible.

Study design
The study was an open-label randomised controlled trial, which was carried out in 34 European and Australian centres. The treatment groups were stratified according to the major sites of disease, gender, and performance status. However, the method of randomisation was not described. The maximum length of follow-up was 1 year. Only 292 patients were deemed "eligible" for treatment, having protocol-specific diagnosis of untreated, advanced, metastatic melanoma with no central nervous system involvement. Only 280 patients actually received at least one dose of study medication, thus making them "treated eligible". Loss to follow-up was due to the patients' death.

Analysis of effectiveness
The clinical analysis was performed on an intention to treat (ITT) basis, although median survival for "eligible" and "treated eligible" patients was also given. The primary health outcome assessed was the median overall survival time, based on Kaplan Meier estimates, and the hazard ratio (HR). The mean survival in the ITT group was also calculated. The groups were shown to be statistically similar in terms of the age, gender, performance status, and disease site at baseline.

Effectiveness results
The median survival in the ITT population was 6.4 months in the DTIC group and 7.7 months in the TEM group (HR 1.18; 95% confidence interval: 0.92 - 1.52, p=0.20).

The mean survival was 8.6 months in the DTIC group and 9.6 months in the TEM group.

Clinical conclusions
The two treatments were not statistically different in terms of the main outcome (survival), although TEM had a better mean and median survival. In terms of the secondary outcomes, the effectiveness analysis showed that TEM was slightly more effective than DTIC.

Methods used to derive estimates of effectiveness
The authors made several assumptions concerning the effectiveness analyses in order to support the trial entry criteria.

Estimates of effectiveness and key assumptions
Several assumptions were made, of which only two are given here. First, the authors assumed that all patients received oral anti-emetics before each daily treatment. Second, they assumed that patient survival after the development of progressive disease was the same, independent of the initial therapy.
Measure of benefits used in the economic analysis
The benefit measure used in the economic analysis was the incremental mean survival (in days and years) of TEM over DTIC. It was derived directly from the effectiveness analysis. The quality of life was not calculated because, at 12 weeks, there were only data available for 31 patients in the DTIC group and 50 patients in the TEM group, due to disease progression and death.

Direct costs
Discounting was irrelevant since all the costs occurred within one year. The unit costs and the quantities of resources used were reported. The cost/resource boundary of the study did not reflect the societal perspective adopted in the analysis. The health service costs included were for the following:

- the direct costs of the drugs,
- durable goods (pharmacy preparation and disposable supplies),
- professional services (physician visits and nursing time),
- pre-treatment laboratory monitoring (complete blood cell count, differential, and platelet; serum chemistries; chest x-ray and interpretation), and
- non-medical direct costs (family or companion lost wages per half day per office visit or therapy).

The costs of adverse events were not included because no adverse events occurred. It was assumed that the evaluation costs incurred to determine whether the examined therapy was appropriate, were excluded. Protocol-specific costs, such as radiological imaging, were not included either. The costs of palliative care after the development of progressive disease were assumed to be the same for both treatments. The resources were estimated using data from the trial, which were gathered from 16 July 1995 to 25 February, 1997. The costs were estimated using actual data, which were derived from the average wholesale prices for drugs and from current reimbursement rates. The price year was 1999.

Statistical analysis of costs
No statistical analyses of the costs were conducted, although the authors referred to "average" costs.

Indirect Costs
It was assumed that the indirect costs did not differ between the treatments.

Currency
US dollars ($).

Sensitivity analysis
Several sensitivity analyses were performed to take into account the variability in the data. The parameters varied included the DTIC cost estimates (high- and low-cost scenarios), the TEM cost ($1,000 instead of $1,500), and median (instead of mean) survival. High DTIC costs included the preparation of the intravenous infusion by the pharmacy and non-medical direct costs. The low estimate included 1-day infusion at 850mg/m2. A further analysis was also performed to assess the relative chance that the incremental cost-effectiveness ratio of TEM over DTIC was below the commonly used threshold of $50,000 per life-year. The type of analysis used was not reported.

Estimated benefits used in the economic analysis
The incremental mean survival of TEM over DTIC was 32 days or 0.087 years.
Cost results
The total cost per treatment cycle was $975 for DTIC and $1,860 for TEM. The average cost per patient was $3,697 for DTIC and $6,902 for TEM.

Synthesis of costs and benefits
The cost and the survival (in days or years) were combined by conducting an incremental cost-effectiveness analysis of TEM over DTIC. In the base-case, the incremental cost per additional life-day was $101 and the incremental cost per additional life-year was $36,990. The lower and upper limits of the 95% confidence interval, calculated around the difference in survival among the treatments, was -$65,180 (meaning that DTIC was dominant, being more effective and less costly) and $18,670. Sensitivity analyses showed that the incremental cost-effectiveness ratio was sensitive to the DTIC and TEM cost estimates, but not sensitive to the median survival estimates. It was stated that in "60% of the simulations", the incremental cost per life-year of TEM over DTIC was below the threshold of $50,000.

Authors' conclusions
Temozolomide (TEM) proved to be as safe and effective as single-agent dacarbazine (DTIC), with a trend towards greater survival and an acceptable cost per life-year.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the interventions to be compared was clear. DTIC represented the standard treatment and TEM was proposed for patients with advanced metastatic melanoma. You should assess whether they represent widely used health technologies in your own setting.

Validity of estimate of measure of effectiveness
The analysis of effectiveness used a large, multinational, randomised controlled trial, which appears to have been appropriate for the study question. Power calculations were performed in the planning phase, and the patient groups were shown to be comparable at analysis. The clinical basis for the effectiveness analysis was ITT. These issues enhanced the internal validity of the study. However, the method of randomisation was not reported.

Validity of estimate of measure of benefit
The benefit measure was derived from the effectiveness analysis. A benefit measure reflecting patients' preferences for quality of life was not used, due to the insufficient data obtained from the sample.

Validity of estimate of costs
The cost analysis was intended to reflect the societal perspective, but it was assumed that the indirect costs did not differ between the treatments. However, there was a lack of clarity in that the authors referred to a cost of 850 per half day for the cost of a patient's companion, including it in the sensitivity analysis as "direct" non-medical costs. A reference was provided, but no explanation was given for the origin of this cost. Therefore, in the base-case, only cost items relevant to the health providers were included in the analysis. Although the costs were treated deterministically, several sensitivity analyses were conducted and different cost scenarios were assumed. The unit costs and the quantities of resources used were reported separately. Some cost items were omitted from the analysis because they were assumed to be the same in both treatment groups. Finally, it was unclear how the simulations were conducted in order to account for uncertainty in the cost-effectiveness.

Other issues
The authors noted that an incremental cost-effectiveness analysis was conducted, although the main effectiveness outcome was not statistically different between the interventions. In this case, some could argue that a cost-minimisation analysis should have been conducted, but the issue is still controversial. The authors did not compare their findings with those from other studies. The issue of the generalisability of the study results to other settings was
implicitly addressed by performing sensitivity analyses on several variables, assuming different scenarios. The authors’ conclusions were in keeping with the study population.

**Implications of the study**
The authors point out that the cost-effectiveness of TEM was sensitive to some assumptions about the indirect costs and practice style of DTIC delivery. This, in turn, means that the adoption of the perspective of the study can be crucial. The authors also made the interesting observation that "TEM for metastatic melanoma illustrates the tension confronting providers choosing between similar agents that markedly differ in convenience and costs".

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