Cost-effectiveness analysis of antifungal treatment for patients on chemotherapy
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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
Three strategies for the treatment of invasive fungal infections in neutropenic patients were examined. The first strategy was prophylactic fluconazole, in which the patient received fluconazole (400 mg/day orally) concurrently with the start of chemotherapy. The second strategy was empirical amphotericin B, in which the patient was given intravenous amphotericin B when a persistent fever of 38 degrees C or higher was observed for 48 hours or more upon administration of an appropriate broad-spectrum antibiotic therapy and in the absence of any obvious source of fever (e.g. resistant bacterial infection abscess or infection with atypical micro-organisms). The third strategy was no prophylaxis, in which a patient was administered micafungin (MCFG) intravenously when fungal culture results strongly suggested fungal infections without any preceding administration of antifungal agents.

Type of intervention
Primary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of 40-year-old patients who were diagnosed for AML defined as French-American-British types M0 to M7.

Setting
The setting was a hospital. The economic study was carried out in Japan.

Dates to which data relate
The effectiveness data were derived from studies published between 1982 and 2002. No dates for the resource use data were given. The price year was not reported.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of published studies and some authors' assumptions.

Modelling
A decision model appears to have been used to assess the costs and benefits of the alternative strategies, but details of the model were not provided. The time horizon of the analysis was the period between the start of induction chemotherapy for AML and the time of complete remission or death.

Outcomes assessed in the review
The outcomes estimated from the literature were:

the probability of fungal infection, the probability of adverse effects, and the rate of death from fungal infection for the fluconazole strategy;

the probability of adverse effects and the rate of death from fungal infection for the empiric amphotericin B strategy;

the probability of fungal infection and the rate of death from fungal infection for the no prophylaxis strategy;

the rate of complete remission and the rate of death with MCFG; and

life expectancy with and without AML.

Study designs and other criteria for inclusion in the review
A review of the literature was carried out to identify relevant primary studies. Only clinical trials or reviews of clinical trials were included. Studies were excluded if the patients were not between 35 and 45 years of age, if the patients underwent bone marrow transplantation, or if the clinical outcomes were not recorded accurately. They were also excluded if the amount of an investigated agent administered was not comparable to that of the agent investigated in the present study. Clinical data for the fluconazole strategy and the no prophylaxis strategy were derived from randomised clinical trials, while clinical results for the empiric amphotericin B strategy were taken from non-randomised studies and reviews since there was a lack of randomised trials. All-cause mortality was obtained from data for the general population mortality from 2002, published by the Ministry of Health, Labour, and Welfare of Japan.

Sources searched to identify primary studies
MEDLINE was searched between 1966 and 2003 for English-language studies. The keywords used were "fungal infection", "haematological malignancy", "fluconazole", "Amphotericin B", "antifungal", "neutropenia", "immunocompromised" and "leukaemia".

Criteria used to ensure the validity of primary studies
The selection of randomised clinical trials should have ensured a high internal validity of the primary estimates. Data derived from non-randomised studies could be considered slightly less robust.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
Twenty-three primary studies provided the clinical data.

Methods of combining primary studies
The primary estimates were combined through calculation of the weighted averages.

Investigation of differences between primary studies
Not reported.

Results of the review
With the fluconazole strategy, the probability of fungal infection was 0.076 (range: 0.023 to 0.089) and the probability of adverse effects was 0.019 (range: 0.023 to 0.032). The rate of death from fungal infection was 0.238 (range: 0.091 to
1.000).

With the empiric amphotericin B strategy, the probability of adverse effects was 0.147 (range: 0.000 to 0.667) and the rate of death from fungal infection was 0.269 (range: 0.000 to 0.300).

With the no prophylaxis strategy, the probability of fungal infection was 0.157 (range: 0.028 to 0.205) and the rate of death from fungal infection was 0.285 (range: 0.148 to 1.000).

With MCFG, the rate of complete remission was 0.606 (range: 0.358 to 0.700) and the rate of death was 0.059 (range: 0.052 to 0.071).

Life expectancy (at 40 years of age) was 3.4 years (range: 2.9 to 3.8) with AML and 39 years (range: 33 to 43) without AML.

Methods used to derive estimates of effectiveness
The authors made some assumptions concerning the clinical outcomes associated with MCFG.

Estimates of effectiveness and key assumptions
It was assumed that the death rate from fungal infection associated with MCFG would be 0.238 (range: 0.000 to 1.000) and that there would be no adverse events associated with MCFG.

Measure of benefits used in the economic analysis
The summary benefit measure used in the economic analysis was life expectancy. This was estimated using the decision model. Disease-free survival was defined as the time from the first complete remission to the date of relapse or death from any cause. Relapse was defined as a recurrence of AML after the first complete remission. The life-expectancy with AML was calculated from disease-specific survival data using the declining exponential approximation of life expectancy method. Discounting was not applied.

Direct costs
The perspective adopted in the analysis of the costs was not explicitly stated, but it might have been that of the third-party payer. The cost items considered were hospitalisation, medical procedures (including chemotherapy), laboratory, medications other than antifungal agents, nutrition, transfusions, antifungal agents (oral fluconazole, empiric amphotericin B, and MCFG), and death from any cause. The unit costs were not presented separately from the resource quantities. Resource use during hospital stay was estimated from a sample of claims from 30 patients at a teaching hospital in Japan. Drug consumption followed the recommended duration of therapy. The approach used to calculate the fixed costs was reported. Similarly, the costs associated with death were based on those of deceased patients and were calculated as the weighted average of all the costs paid during the final week before death. The costs were obtained from reimbursement rates regulated by the government of Japan. Given the short timeframe of the analysis, discounting was not relevant and was not applied. The price year was unclear.

Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
The indirect costs were not taken into consideration.

Currency
Japanese yen (JPY). These were converted into US dollars ($). The exchange rate for March 2003 was $1 = JPY 120.
Sensitivity analysis
Univariate sensitivity analyses and threshold analyses were carried out to assess the robustness of the cost-effectiveness estimates to variations in the clinical and economic inputs. Ranges of values used in the sensitivity analysis were derived from the literature, and were supplemented with experts' opinions when published variances were not available.

Estimated benefits used in the economic analysis
The life expectancy was 23.12 years with no prophylaxis, 23.16 years with empiric amphotericin B, and 24.08 years with prophylactic fluconazole.

Cost results
The cost per patient was $25,400 with both no prophylaxis and empiric amphotericin B, and $25,900 with prophylactic fluconazole.

Synthesis of costs and benefits
An incremental cost-effectiveness ratio (ICER; i.e. incremental cost per life-year saved) was calculated to combine the costs and benefits of the alternative strategies.

The ICER of prophylactic fluconazole was $625 in comparison with no prophylaxis and $652 in comparison with empiric amphotericin B.

The results of the sensitivity analysis showed that the ICER for prophylactic fluconazole remained the preferred strategies in all but two cases, in which it was dominated by empiric amphotericin B. The first case was when the probability of fungal infection without prophylaxis fell below the threshold value of 0.028 (it was 0.157 in the base-case). The second case was when the rate of death from fungal infection was set at 100%.

Authors' conclusions
Oral fluconazole prophylaxis could be the antifungal treatment strategy of choice, compared with empirical amphotericin B or no prophylaxis, for patients undergoing chemotherapy in Japan. However, this conclusion relied on a key assumption: in the case of the no prophylaxis strategy, antifungal agents would not be administered until fungal culture was found to be positive, and that the resultant delay in antifungal treatment led to higher mortality. It was also noted that use of the empirical amphotericin B strategy may be preferable at centres where mould infections such as Aspergillus species and drug-resistant Candida species are frequently encountered. The sensitivity analysis indicated that the empirical amphotericin B strategy could be the preferred strategy in settings where the incidence of fungal infections without prophylaxis is low.

CRD COMMENTARY - Selection of comparators
The authors justified their choice of the comparators. The selection of the three strategies appears to have been appropriate given that it considered a full range of alternatives such as prophylaxis, empirical therapy and no prophylaxis. In addition, the dosages used were clearly described. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence was obtained from a review of the literature carried out on an electronic database. The search strategy was reported. The inclusion and/or exclusion criteria used to select the primary studies were explicitly stated and the approach used to combine the primary estimates was also described. The search attempted to include only randomised studies in order to ensure a high internal validity of the primary estimates. However, non-randomised studies also had to be used given the lack of randomised studies on empirical therapy. The issue of heterogeneity among the primary estimates was not investigated. Some assumptions were also required because of a lack of published
evidence on some key clinical parameters. The issue of uncertainty was addressed in the sensitivity analysis.

**Validity of estimate of measure of benefit**
Life-years were the most appropriate benefit measure because they capture the impact of the intervention on expected survival, which is the most relevant dimension of health for patients on chemotherapy. The impact of the interventions on quality of life was not addressed. The use of life-years will permit comparisons with the benefits of other health care interventions.

**Validity of estimate of costs**
The authors did not explicitly report the perspective of the analysis. However, the sources of the cost data would appear consistent with a third-party payer perspective, since reimbursement rates were considered as the source of the costs. Resource consumption was based on recommended dosages and a sample of patients admitted to a teaching hospital. The unit costs were not presented separately from the quantities of resources used, which might limit the possibility of replicating the analysis in other settings. Statistical analyses of the costs were not performed. The authors did not report the price year, which will hinder reflation exercises in other time periods.

**Other issues**
The authors compared their findings with those from other studies. In particular, it was noted that the results of their study contrasted with those of a meta-analysis in which oral fluconazole prophylaxis or empirical amphotericin B did not reduce mortality for cancer patients with neutropenia compared with a no-prophylactic strategy. The authors stated that this might have been due to the fact that, in the meta-analysis, patients in the control group (no prophylaxis) could receive some antifungal agent. In terms of the generalisability of the study results to other settings, the authors acknowledged that the current findings could not be extrapolated to other countries given the peculiarity of the Japanese health care system. The external validity of the study was improved by performing selected sensitivity analyses.

The authors noted some limitations of the analysis. First, the uncertainty surrounding the probability of fungal infection (which was addressed in the sensitivity analysis). Second, the short timeframe (which precludes drawing conclusions about the cost-effectiveness of the alternative strategies in the long run). Finally, the assumption that fungal infections could be effectively controlled by MCFG without further treatments.

**Implications of the study**
Within the limitations of the modelling analysis, the study results supported the use of oral fluconazole as prophylaxis against fungal infections in patients on chemotherapy.

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**Other publications of related interest**
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