Imipenem versus targeted therapy in cancer patients
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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
A broad-spectrum antibiotic (imipenem) therapy was compared with a targeted antibiotic therapy (according to the pathogen isolated) for the treatment of cancer patients who developed infection. The dosage of imipenem was 2g daily given intravenously. Four antibiotics were selected for the targeted therapy. These were to be used alone or in combination according to the type of pathogen(s) detected.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised adult cancer patients with fever and other signs of infection. For example, bacteraemia, sepsis, lower respiratory tract infection, urinary tract infection, skin, soft tissue or wound infection, or intra-abdominal infection. The study excluded those who were neutropenic, had severely impaired renal function, or whose pathogen was resistant to imipenem. In addition, patients who had received other antibiotics in the 3 days prior to enrolment were also excluded.

Setting
The setting was secondary care. The economic study was carried out in Belgium.

Dates to which data relate
The costing of medicines used unit prices from 1995. No other dates were given.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
The costing was undertaken on the same patient sample as that used in the effectiveness study. The resource use data were collected prospectively.

Study sample
One hundred and ninety-seven cancer patients were enrolled in the study and received imipenem for the first 72 hours. Of these, 152 had microbiologically documented infections and were, therefore, eligible for subsequent randomisation to either continue on imipenem or switch to the targeted therapy. Only 122 patients were actually randomised (61 to...
each arm). The other 30 were excluded for reasons such as having a resistant pathogen, treatment failure, death and early discharge. The authors explained that this sample was restricted to non-neutropenic patients and was not meant to be representative of febrile cancer patients in general. No power calculations to determine sample size were reported.

**Study design**
The 122 patients took part in a randomised controlled trial. The patients were randomised using consecutively numbered sealed envelopes. The duration of follow-up was not explicitly stated, although the patients received antibiotic treatment for about 10 days on average and the economic study did include the cost of adverse events and subsequent extensions of stays in hospital. The number of centres involved was not stated. It was also not stated whether the participants and/or researchers were blind to the randomisation.

**Analysis of effectiveness**
It was not reported whether the data were analysed on an intention to treat basis, although the analysis presented was based on two treatment groups with 61 patients in each. The primary health outcomes included the rate of clinical response to antibiotic regimen, superinfection and side effects. It was unclear whether the groups were comparable at baseline in terms of their age and gender, as these data were not given. However, the two groups appear to have been similarly distributed across the possible sites of infection, such as bacteraemia, lower respiratory tract and urinary tract.

**Effectiveness results**
Overall, a significantly higher cure rate was found in the imipenem patients (88.8%) than in the targeted therapy group (72.1%), (p=0.025). In Gram-negative infections, the response rates were 74% with imipenem and 72% with targeted therapy, (p=0.99). The response rate in Gram-positive infections was higher in the imipenem group (78.5%) than in the targeted therapy group (67.8%). This difference was not statistically significant, (p=0.39).

Bacterial superinfections occurred in 9 patients (14%) in the imipenem group and in 10 patients (16%) in the targeted therapy group, (p>0.50). Fungal superinfections occurred in 11% of imipenem patients and 17% of targeted therapy patients, (p=0.32).

Thirty per cent of the patients on imipenem experienced side effects, compared with 27% of those on targeted therapy, (p>0.05).

**Clinical conclusions**
Overall, imipenem therapy had a higher efficacy than targeted therapy.

**Measure of benefits used in the economic analysis**
The summary benefit measure used in the economic analysis was patients cured of bacterial infection.

**Direct costs**
The analysis included the hospital costs of all the antibiotics used, including the cost of imipenem (for 72 hours) before randomisation. The drug costs were computed by counting the number of patient days on each drug and adjusting these downward for dose reductions due to renal failure. The adjusted patient days were then multiplied by a price per day. The total number of patient days for each drug was reported separately. The drug prices were published by the Belgian social security office and related to 1995. No date was given for the resource use data.

The costs of adverse events (including subsequent extensions of hospital stays) and further antibiotic, antiviral or antifungal treatment, were also included. Fewer details were reported on these elements. Certain cost components were excluded as they were thought to be common to both alternatives. These included the infusion costs unrelated to adverse events or nursing time.
The study reported the average costs relevant to a hospital setting. Discounting was irrelevant due to the short timeframe involved.

**Statistical analysis of costs**
Statistical tests were carried out on the mean values of some resource use components, but not on the overall costs or cost per patient.

**Indirect Costs**
No indirect costs were included in this analysis.

**Currency**
Belgian francs (Bfr). There were no conversions to any other currencies.

**Sensitivity analysis**
The authors examined the possibility of giving other antibiotics instead of ciprofloxacin to the targeted therapy group. They recalculated the cost of initial treatment in the targeted therapy group by substituting the price of five other drugs for that of ciprofloxacin. However, as pointed out by the authors, this analysis is of limited value as it excludes non-price factors that influence cost, such as the duration and failure rate of treatment.

**Estimated benefits used in the economic analysis**
In this study, 10 additional patients (out of 61) were cured of their infection on imipenem therapy as compared with targeted therapy, (p=0.025). There was no statistically significant difference in the incidence of side effects in the two groups.

**Cost results**
The total cost of treating the imipenem group was Bfr 1,851,700.

The total cost of treating the targeted therapy group was Bfr 2,567,500.

These included the costs related to initial treatment failure and superinfection.

**Synthesis of costs and benefits**
The incremental cost of imipenem treatment compared with targeted therapy was Bfr -71,580 per extra patient cured. In this case, this means that the imipenem therapy was both less expensive and cured more patients, and therefore dominated the targeted therapy option. The authors noted that in Gram-positive infections, targeted therapy was less expensive, though not necessarily cost-effective.

**Authors' conclusions**
Imipenem therapy costs less than targeted therapy and is significantly more efficient.

**CRD COMMENTARY - Selection of comparators**
Neither of the two alternatives was explicitly selected as the comparator. The authors suggested that they chose these two alternatives on the basis that the use of broad-spectrum antibiotics is more commonly used and targeting therapy to the identified pathogens is also a sensible approach. You will have to compare these with the treatment options in your own setting.
Validity of estimate of measure of effectiveness
Generally, the study design and study population appear to have been appropriate for examining the use of antibiotic therapy in non-neutropenic cancer patients. The two groups appear to have been comparable at baseline in terms of the sites of bacterial infection. However, it was unclear whether they were similar in terms of their age and gender. This could be a weakness in the study if response to antibiotic therapy is linked to age and/or gender. A further limitation was the apparent lack of blinding to the treatment regimens. For example, the authors found a tendency (though not significant) towards a longer treatment duration in the targeted therapy group, compared with the imipenem group. Without blinding, this could be explained by the nurses’ perceptions of the effectiveness of different antibiotic drugs.

Validity of estimate of costs
This analysis included most relevant costs. For the initial antibiotic therapy, the overall resource use quantities were reported and these data could be generalisable to other settings. The authors correctly excluded the costs of intravenous administration of antibiotics, as they stated all patients were automatically put on intravenous infusion. Thus, there was no difference in these costs between the two groups.

Other issues
In their discussion, the authors suggested that the most efficient resource allocation would be to shift to targeted therapy in Gram-positive infections, because they showed this to be the cheaper option. However, they also showed it to be less effective, though not significantly so. In such a case, no statement can be made about the efficiency of shifting to the less costly option without examining whether the reduced cost is “worth” the reduced effectiveness. In order to substantiate a recommendation such as this, a separate cost-effectiveness analysis should be carried out, as there would presumably be additional laboratory costs to identify a Gram-positive or negative bacterium, which would not be necessary were all patients automatically allocated imipenem therapy.

Finally, although it was not part of the economic analysis, this paper presented interesting results and a discussion about the possible effect of this trial on the hospital microbial ecology.

Implications of the study
The authors consider the use of imipenem throughout the whole infectious episode to be a better approach than switching to targeted therapy once the strains have been isolated. As suggested in the commentary, there may be a need for further research about the cost-effectiveness of a strategy for Gram-positive infections.

Source of funding
None stated.

Bibliographic details

PubMedID
9916899

Original Paper URL
http://www.sciencedirect.com/science?_ob=ArticleURL&amp;_udi=B6T7H-3VB32PH-3
&_user=126317&_coverDate=11%2F30%2F1998&_rdoc=3&_fmt=summary&_orig=browse
e&_srch=%23toc%2325059%2321998%2323998999995%232340656!&&_cdi=5059&_sort=d&_doc anchor=&&wchp=dGLbVtb-lSztb&_acct=C00Indexing Status
Subject indexing assigned by NLM
MeSH
Anti-Bacterial Agents /therapeutic use; Bacterial Infections /classification /drug therapy /epidemiology; Fever; Gram-Negative Bacterial Infections /drug therapy; Gram-Positive Bacterial Infections /drug therapy; Humans; Imipenem /therapeutic use; Mycoses /epidemiology; Neoplasms /complications; Neutropenia; Thienamycins /therapeutic use

AccessionNumber
21999006526

Date bibliographic record published
31/12/2002

Date abstract record published
31/12/2002