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Gemcitabine: clinical and economic impact in inoperable non-small cell lung cancer

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This study assesses retrospectively the clinical and economic impact of gemcitabine monotherapy on the management of inoperable stage III/IV non-small cell lung cancer in Germany. Based on current methods of clinical practice and using the best outcome data available, the costs and benefits of gemcitabine were compared to a dual therapy (ifosfamide/etoposide). While the two treatments showed broadly equivalent efficacy in terms of tumour response rate and survival, a cost analysis showed the potential for savings with gemcitabine. These largely related to hospital hotelling costs, due to the fact that gemcitabine may be given as an out-patient therapy. Further savings were found in investigative procedures and the management of treatment toxicity. Excluding the cost of the chemotherapy, gemcitabine was associated with potential savings of DM3,026 over two cycles of therapy, which included a 40% decrease in hospitalization costs and a 54% decrease in the cost of managing adverse events. We conclude that gemcitabine monotherapy could offer considerable cost savings while offering the potential for improved quality of palliative treatment compared to existing in-patient treatments, and it may have a place in shifting care from an in-patient to an out-patient setting in line with recent health care reforms.

Introduction

Lung cancer is the most common malignancy in the Western world, and its prevalence is increasing. About 80% of lung cancer patients are diagnosed with non-small cell lung cancer (NSCLC). Surgery offers the best chance of cure if the disease is recognized early, but most patients present with advanced disease unsuitable for potentially curative therapy (Figure 1). The overall prognosis is poor, with a 5 year survival rate of less than 10%.[1]

It is clear therefore that treatment is palliative for the majority of NSCLC patients. Tumour response to chemotherapy or radiotherapy is routinely assessed as a measure of treatment efficacy, but as treatment rarely prolongs life by more than a few months, symptom relief and improved well-being are actually the primary end-points.[2,3] One of the main difficulties with chemotherapy is to achieve an acceptable balance between the toxicity of treatment and the impact it will have on these end points. When the intention is curative, high levels of toxicity are more easily justified, but for palliative treatment

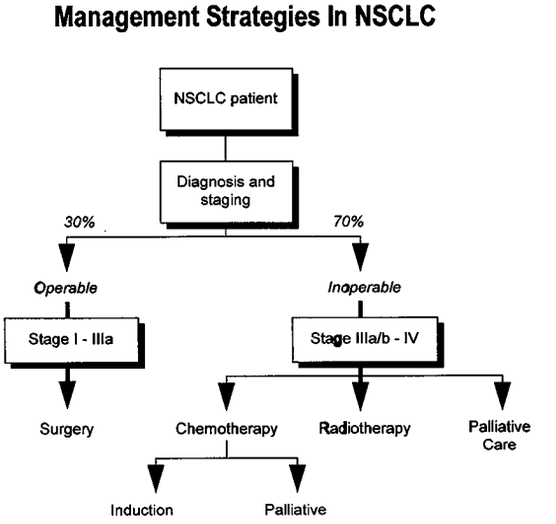

Figure 1. Treatment strategies in the management of NSCLC.

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less toxic regimens are preferred.[3] From the patient's point of view, therefore, the avoidance of toxicity is also an important criterion for treatment success, and a valid effectiveness end point. The issue for clinicians is to select a treatment which combines good clinical response (i.e. symptom relief) with good patient acceptability.

In addition to clinical benefits, the economic implications of alternative health care interventions are now playing an increasing role in the decision-making process. New therapies are particularly prone to close economic scrutiny, to ensure that the specific benefits they offer are sufficient to justify their cost. This has particular relevance in Germany, where recent health care reforms are promoting a more thorough approach to efficiency in health care delivery.[4] The hospital reimbursement system is now undergoing dramatic changes. Reimbursement based on daily rates per patient stay in hospital (*per diem*) will be abolished by 1996. Hospitals previously free of cost containment had to begin operating within capped budgets in 1993, and this in turn will encourage out-patient treatment. As chemotherapy is currently mainly an in-patient treatment, the consequences for cancer chemotherapy will be considerable.

The purpose of this study was to assess the use and economic impact of a new oncolytic agent, gemcitabine, currently in clinical development for the treatment of prostate, ovarian, non-small cell lung and other cancers, as monotherapy or combination treatment. In NSCLC, gemcitabine monotherapy has an efficacy which is broadly comparable to current dual chemotherapy combinations and a favourable toxicity profile compared to other chemotherapies.[5] In addition, gemcitabine may be easily administered on an out-patient basis as a 30 min infusion. The chosen comparator for the purposes of this analysis was an ifosfamide/etoposide combination, selected because it has a clinical profile typical of dual chemotherapy regimens used in this indication, but also because of the availability of published data which allowed a reasonable retrospective comparison.

Methods

Treatment efficacy and toxicity

As there is no direct comparison between gemcitabine monotherapy and ifosfamide/etoposide, the analysis was based on an evaluation of retrospective data to generate assumptions regarding the effectiveness and toxicity of the two therapies. In the absence of more meaningful data on symptom relief and patient quality of life, the primary measures of efficacy in palliative treatment, tumour remission, was used as the end point for this analysis. This reflects accepted clinical practice in Germany, where tumour remission is used as a surrogate marker of treatment effectiveness.

In this assessment we selected ifosfamide/etoposide to compare with gemcitabine monotherapy, as a *representative* example of the dual therapy combinations currently employed in Germany. This is because (i) the profile of ifosfamide/etoposide reflects that of other dual therapy regimens, and (ii) data are available in a published form to allow a reasonable retrospective comparison.

Ifosfamide is one of the most potent single agents, as assessed by tumour response rate, in NSCLC.[6,7] The response rate of etoposide is considerably lower but the combination of both achieves a higher response rate than either alone. The available data suggest response rates of 14%–27% for the combination treatment,[8–10] and 22% for gemcitabine.[5] Median survival times are similar, with 8.0 months for the ifosfamide/etoposide combination and 9.4 months for gemcitabine. In conclusion, the two treatment options have broadly comparable efficacy, and this economic evaluation assumed that tumour response was equivalent for both therapies.

A review of the major side effects associated with each treatment, including myelosuppression, nausea and vomiting, alopecia and flu-like symptoms, was also undertaken, together with a detailed analysis of their management. This information was obtained from the published results of both gemcitabine [5] and ifosfamide/etoposide [8] studies. Compared to ifosfamide/etoposide, gemcitabine was shown to have a substantially lower incidence of nausea and vomiting (65% vs 94%), and a very low incidence of alopecia (1% vs 99%). Both of these side effects are of particular concern to patients receiving cancer chemotherapy.[11] Mild flu-like symptoms, reported in 33% of patients receiving gemcitabine, were short-lasting and often relieved by treatment with diclofenac or paracetamol.

In view of the similarity in efficacy between the two treatment options, the analysis was one of cost alone.

Clinical management patterns

Assumptions regarding patient management were based on information obtained from detailed inter-

Ifosfamide and etoposide treatment protocol

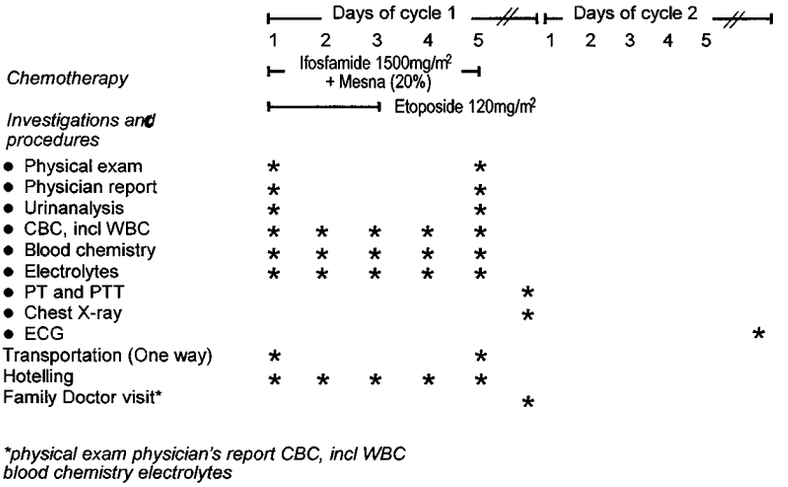

Figure 2. Ifosfamide/etoposide treatment protocol over two cycles of chemotherapy.

Gemcitabine treatment protocol

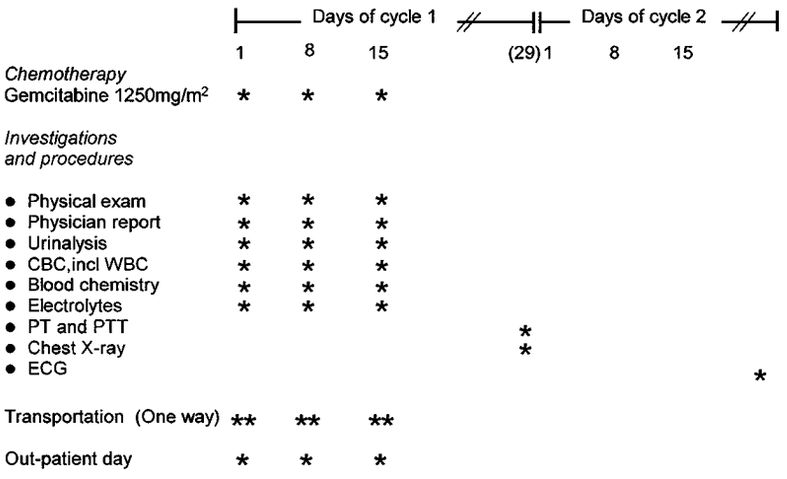

Figure 3. Gemcitabine treatment protocol over two cycles of chemotherapy.

views with practising German oncologists. The management of treatment toxicities was the subject of particularly close scrutiny, the key areas being protocols for managing emesis and febrile leucopenia. Diagnostic and staging procedures in NSCLC are the same for both treatment groups. However,

differences occur during the chemotherapy administration (Figures 2 and 3). For ifosfamide/etoposide it is assumed that the combination will be given on an in-patient basis over 5 days per cycle. This assumption is based on the following factors: (i) necessity of uroprotection during, and after, ifosfamide administration; (ii) improvement of efficacy and tolerance when given over 5 days per cycle; and (iii) hospital *per diem* rate reimbursement system encouraging hospitalization to recoup expenditures for diagnosis and treatment.

It should be noted that the combination ifosfamide/etoposide can also be given on an out-patient basis with a reduced number of treatment days per cycle.

A physical examination is performed at hospital admission and discharge. A complete blood count, blood chemistry, and electrolytes are investigated on a daily basis, and repeated approximately 10 days after discharge by the patient's family doctor. A chest X-ray is performed every 4 weeks, and an ECG every 8 weeks at the hospital.

It was assumed that gemcitabine is administered on an out-patient basis, as a 30 min infusion at weekly intervals on days 1, 8 and 15. While no hospitalization is necessary for treatment administration, a total of 3 out-patient visits would be needed. On each of the treatment days a physical examination, complete blood cell count, blood chemistry and electrolyte are carried out. A chest X-ray is performed every 4 weeks, and an ECG every 8 weeks.

Costs

Costs were calculated per cycle of chemotherapy for both treatment regimens. These were divided into the costs of diagnosis and staging, investigations and procedures (including chemotherapy), delay of chemotherapy, management of leucocytopenia, thrombocytopenia, anaemia, and alopecia, pre-treatment and treatment of nausea and vomiting, treatment of flu-like symptoms, and hospital stay. Accurate hospital investigation and procedure costs are not available in Germany and were assumed to be the same as community sector reimbursement rates.[12] The cost of drugs was calculated using two methods: net wholesale price, and *Rote Liste* price less a hospital discount of 40%. Hospital in-patient and out-patient stay (hotelling) were based on 75% of a typical DM500 *per diem* rate, which has been estimated to reflect fixed costs and overheads.[13] A detailed analysis of these areas allowed determination of the overall management costs associated with gemcitabine compared with ifosfamide/etoposide combined therapy. The cost of gemcitabine was not included in the analysis since this was not known at the time the assessment was performed.

Table 1. Cost (in DM) over two cycles of chemotherapy

Cost element	Ifosfamide/ Etoposide	Gemcitabine
Diagnosis and staging	945.23	945.23
Chemotherapy administration		
Investigations and procedures	2382.88	1984.02
Hotelling/Out-patient day	3750.00	2250.00
Drug cost (net wholesale price)	2326.00	Unknown
Additional cost (mesna, hydration, administration)	489.50	44.22
Toxicity		
Leucopenia	637.19	164.85
Thrombocytopenia	18.42	31.58
Anaemia	184.31	184.31
Alopecia	100.00	2.00
Nausea and vomiting	316.90	154.72
Flu-like symptoms	0.00	2.98
Hospitalization	0.00	34.50
Total DM	11,150.51	5,798.41*

* Excludes drug cost.

Results

A summary of the estimated costs which will be incurred by both therapeutic options is shown in Table 1. The analysis shows that diagnostic and staging costs are the same for both treatment options, but that major differences occur in the administration costs of chemotherapy. It can be seen that the hotelling element of the in-patient stay accounts for more than 33% of total treatment costs with the ifosfamide/etoposide combination. The cost of managing toxicity, however, is much less, representing less than 15% of the total. Overall, the cost of giving the combined regimen, including the expense of treating associated adverse events, is in the region of DM11,150 over two cycles. The treatment costs with gemcitabine, including the cost of treating toxicity but *excluding the price of gemcitabine,* amounts to DM5,798.

A description of the cost differences excluding the cost of all chemotherapy is shown in Figure 4. This shows that hotelling costs were reduced by

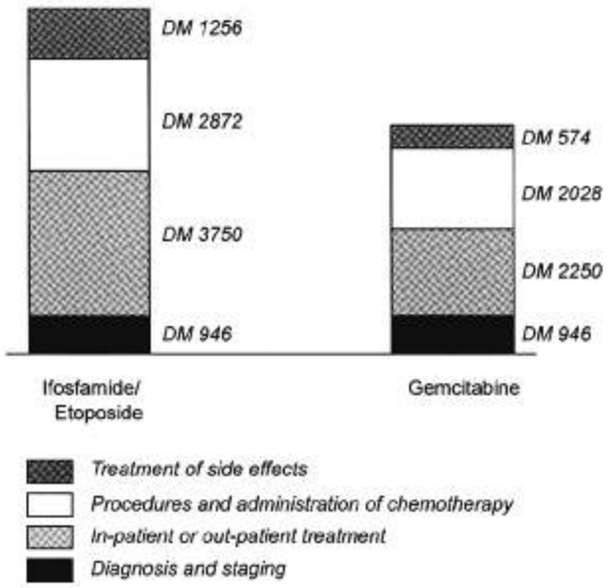

Figure 4. Direct costs of two different chemotherapy options for two cycles, excluding the costs of drugs.

40% under gemcitabine management and the cost of treating toxicity was reduced by 54%. Also, the cost of procedures used in administering therapy was reduced by 30%.

Sensitivity analysis

In order to determine whether the results of the analysis were heavily dependent on any single assumption, a number of key parameters were varied. Varying the base assumptions for the duration and cost of hospital stay was found to have a major impact on the savings produced by gemcitabine. In the original analysis, for example, the same cost was assumed for hospital stay, whether in-patient or out-patient, for both treatment options. However, the net time spent in hospital for a patient treated with gemcitabine is significantly less than for one treated with ifosfamide/etoposide. If it is assumed that an out-patient day equals 50% of the cost of an in-patient day, additional cost-savings are present. In contrast, it could be argued that the ifosfamide/etoposide combination could be given as a 3 day treatment schedule, reducing the number of hospital in-patient days and therefore the overall cost of treatment. Varying other key assumptions showed that the findings of this analysis did not change significantly.

Discussion

The analysis suggests that, excluding the cost of the drug itself, gemcitabine monotherapy has the potential to generate considerable savings compared to an ifosfamide/etoposide combination in the management of inoperable NSCLC. These are mainly due to the use of a dosing schedule which allows the drug to be administered over a shorter period of time as an out-patient therapy, thereby saving on hospital hotelling costs. These were shown to be the single largest item of expenditure, which is in line with previous findings.[14] Other cost savings are the result of the superior side-effect profile of gemcitabine, which produces substantially lower myelosuppression, leading to fewer hospitalizations for febrile leucopenia. It also produces a very low incidence of alopecia compared to the ifosfamide/etoposide combination, and a lower incidence of nausea and vomiting. The savings suggested by the model are probably an underestimate, since it was assumed that an out-patient visit costs the same as an in-patient stay.

Gemcitabine also offers considerable advantages in terms of its toxicity profile, an area which is of prime importance to the patient. Although the choice of one palliative treatment over another is initially based on tumour response, clinicians choosing between two therapies of equal efficacy are more willing to make a trade-off against other patient benefits, particularly with regard to drug toxicity. This is an important factor for treatment success, and will, in some cases, determine whether a patient receives treatment or not. Less toxic chemotherapy may therefore broaden the range of patients who could benefit from its use, and improve the quality of patient survival. In addition, the availability of gemcitabine, an effective but less toxic agent, offers the possibility of treatment combinations where oncologists wish to pursue a more aggressive management strategy with more curative intent.

Although it is not possible to evaluate these benefits in monetary terms, it is important to remember that they occur and are *in addition* to the cost savings which gemcitabine has the potential to generate.

A legitimate criticism of economic analyses is their relevance to clinical practice. This study has revealed the possibility of cost savings with gemcitabine, largely generated as a result of an assumed shift from in-patient to out-patient care. It could be argued, however, that these savings may not be achievable as direct financial savings in a practical

clinical context. For example, the overhead cost of maintaining a hospital bed may remain unchanged whether it is occupied for a few hours (out-patient) or a whole day (in-patient). Similarly, a decrease of cycle duration from 5 to 3 days is of no value unless this can be utilized effectively by the hospital. In order to address such potential criticisms and examine the impact of therapy on ward management, a separate analysis of the two regimens was undertaken. This examined infrastructure and management costs in an in-patient hospital setting and evaluated the potential impact of introducing an oncolytic like gemcitabine which could be administered on an out-patient basis. The results of this model (not reported here) confirmed the potential for cost savings and the increased efficiency of cancer treatment and care in a hospital environment.

The analysis shows that gemcitabine is a cost-effective alternative to dual agent chemotherapy regimens currently employed in the palliative treatment of advanced NSCLC. It suggests that gemcitabine has the potential to produce significant savings in health care expenditure over the two cycles of therapy considered in this analysis. In addition to these savings of DM3,026 over two cycles, it provides further benefits in terms of improved well-being and potential gains in quality of life as a result of decreased toxicity, which is of major importance in palliative treatment.

A substantial portion of such cost savings emanate from the potential switch to out-patient treatment. German hospitals are currently reimbursed on a *per diem* rate, and under this system it is unlikely that the savings shown here will be achieved. However, the new *Gesundheitsstrukturgesetz* (GSG) foresees the introduction of a cost-per-case system and a shift towards out-patient care. Drugs such as gemcitabine could therefore act as enabling technologies, allowing physicians and other health care professionals to deliver superior patient care at a potentially lower cost to the social security system.

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