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ORIGINAL PAPER

Comparative cost-minimisation of oral and intravenous chemotherapy for first-line treatment of non-small cell lung cancer in the UK NHS system

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Abstract The National Institute for Health and Clinical Excellence recommends vinorelbine (VNB), paclitaxel, docetaxel, and gemcitabine in the treatment of non-small cell lung cancer. An economic model was prepared to determine the comparative cost of these agents, including the new oral formulation of VNB from a United Kingdom National Health System perspective. Clinical effectiveness was determined from published trials. Costs of drug acquisition, administration, toxicity management, and patient transportation costs were calculated from reference publications. A Markov model was used to estimate the cost per patient over 52 weeks. Intravenous VNB, gemcitabine, paclitaxel, and docetaxel incur annual follow-up costs of £3,746, £5,332, £5,977, and £6,766, respectively, while oral VNB with outpatient administration on d1, and self-administration at home on d8 every 21 days has a cost per patient per year of £2,888. Oral VNB allows further hospital resources savings.

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Introduction

The National Institute for Health and Clinical Excellence (NICE) Clinical Guideline on the diagnosis and treatment of lung cancer, published in February 2005 [1], recommends the third-generation agents vinorelbine (VNB), paclitaxel, docetaxel, and gemcitabine as first-line chemotherapy options for advanced non-small cell lung cancer (NSCLC) patients. Since the Guideline was published, the oral formulation of VNB discussed in the Health Technology Appraisal report has been introduced in the United Kingdom. The Appraisal stated that, ''This oral version will reduce the costs of administration (no infusion will be needed, thereby reducing the workload on nursing and pharmacy) and the number of visits needed, though specialist monitoring of response and side-effects will still be needed. The net effect will be to increase the cost-effectiveness of VNB and reduce inconvenience to patients'' [2]. A Markov model previously published from a French Healthcare perspective [3] was used to compare the annual follow-up cost of the agents from a United Kingdom National Health System (UK NHS) perspective. This study was the basis of the Scottish Medicines Consortium endorsement for Scottish use of the oral form of VNB [4]. The evaluation took into account costs of drug acquisition, costs of staff and equipment required for chemotherapy delivery, costs of managing common toxicities, and costs of patient transportation to and from hospital, using standard UK NHS references.

Materials and methods

Agents and administration schedules

The commonly used administration schedules of intravenous (IV) and oral VNB, IV gemcitabine, IV paclitaxel, and IV docetaxel were identified (Table 1) by a consensus group of 15 oncology experts, of different ages, backgrounds and experiences, from all over the United Kingdom.

Clinical data

A literature search from 1990 to 2004 was carried out to determine the effectiveness for each of the four cytotoxic agents used as a single agent in NSCLC, using the Medline, Embase, Pascal, Database of Abstracts of Review of Effectiveness, NHS Economic Evaluation Database, and Health Technology Assessment databases. The largest phase III study for each agent was selected as the primary study: Le Chevalier et al. [5] for VNB, Ten Bokkel Huinink et al. [6] for gemcitabine, Roszkowski et al. [7] for docetaxel, and Ranson et al. [8] for paclitaxel. Additional parameters not documented in these articles were obtained from publications by Crawford [9], Depierre [10], Jassem et al. [11], Perng [12], and Anderson et al. [13] (Table 2). The median duration of survival in the primary studies varied between 24 weeks [6] and 31 weeks [5]. However, the studies show slight differences in survival between new cytotoxic agents and older or palliative treatments. In the context of the available published data, and in accordance with the view of NICE, a conservative assumption of a non-difference in therapeutic efficacy was made between chemotherapies in the model. A cost-minimisation study was carried out by allocating to the 13 regimens the published data for VNB in the Le Chevalier et al. [5] study. Median values for outcomes (times and rates) have been converted into equivalent weekly probabilities using the DEALE and actuarial method [14, 15]. The cost of treatment was closely estimated using a 52-week modelling period, so for each agent the chemotherapy cost entered in the model was only for patients remaining on treatment.

The tolerance profile from the clinical studies varied between cytotoxic agents. The main variations concerned haematological toxicity, in particular the

Table 1 Therapeutic options. *IV* Intravenous

Strategy		Day 1 (mg/m^2)	Day 8 (mg/m^2)	Day 15 (mg/m^2)	Day 22 (mg/m^2)	Day 29 (mg/m^2)	Day 36 (mg/m^2)	Day 43 (mg/m^2)
Oral vinorelbine 60–80 mg/m^2	D1–D8	60	60		80	80		80
	Weekly	60	60	60	80	80	80	80
Oral vinorelbine 60 mg/m^2	D1–D8	60	60		60	60		60
	Weekly	60	60	60	60	60	60	60
IV vinorelbine 25 mg/m^2	D1–D8	25	25		25	25		25
	Weekly	25	25	25	25	25	25	25
IV vinorelbine 30 mg/m^2	D1–D8	30	30		30	30		30
	Weekly	30	30	30	30	30	30	30
IV gemcitabine	D1–D8–D15	1,000	1,000	1,000		1,000	1,000	1,000
	D1–D8	1,250	1,250		1,250	1,250		1,250
IV docetaxel	DOC	100			100			100
IV paclitaxel	PAC 175	175			175			175
	PAC 200	200			200			200

Table 2 Efficacy and toxicity data issued from literature

Variables	Vinorelbine PO	Vinorelbine IV	Gemcitabine	Docetaxel	Paclitaxel
Drop-outs	8% [5]	8% [5]	7% [6]	19% < SAE [7]	4% [8]
Median time to progression	10 weeks [10]	10 weeks [10]	12 weeks [6]	12.6 weeks [7]	17 weeks [8]
Medial duration of survival	31 weeks [5]	31 weeks [5]	24 weeks [6]	26 weeks [7]	27 weeks [8]
Dose reduction	17% [5]	17% [5]	19% [18]	10% cycles [7]	32% [8]
Febrile neutropenia	4% [11]	4% [5]	1% [19]	11% [7]	10% [8]
Anaemia—thrombopenia	18% [9]	18% [9]	14% [6]	NA	NA
Diarrhoea—constipation	4% [5]	4% [5]	1% [19]	4% [7]	4% [8]
Nausea—vomiting	18% [11]	5% [10]	11% [6]	5% [7]	5% [8]

incidence of febrile neutropenia requiring admission to hospital and thrombocytopenia requiring blood transfusions, diarrhoea, and nausea and vomiting. In the early studies of oral VNB [11], patients were treated without routine anti-emetic prophylaxis and were fasted at the time of dosing; hence the rates of nausea and vomiting are higher in early publications compared to later studies where $5HT_3$ anti-emetic prophylaxis and dosing with a snack were routine, and shown to improve tolerance. The published rates of severe toxicities for each comparator allowed calculation of the costs of managing severe adverse events using NHS reference sources [16–19].

Modelling

The 13 branches that emanate from the decision node represent the competing therapeutic options (Fig. 1). Each of the branches attached to the Markov node corresponds to a so-called Markov state. Six mutually exclusive states of health are defined using exclusively clinical criteria: Induction, Remission with or without dose reduction, Drop-Out, Progression, Death. The smallest common denominator of time was chosen to define the pace of simulation, i.e. weekly cycles. At each course of treatment, patients who die, whose illness progresses or who drop out of the study, have

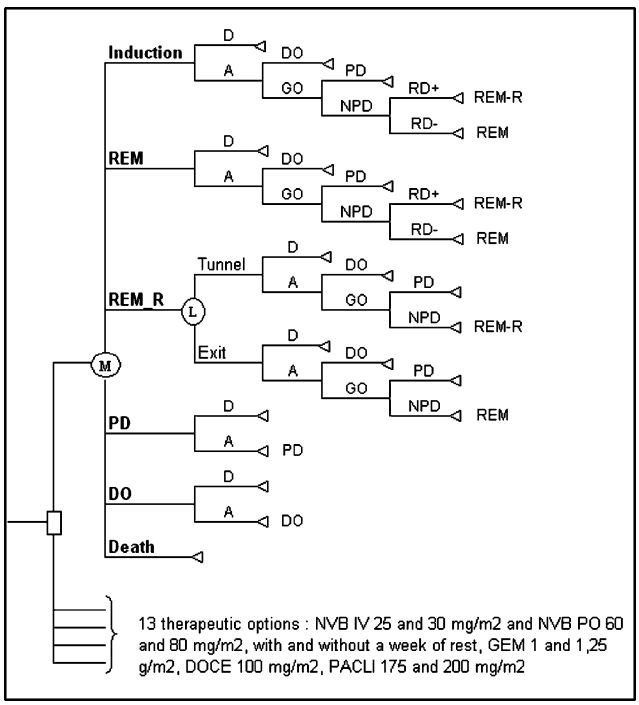

Fig. 1 Simplified Markov model. *REM* Remission without dose reduction, *REM R* Remission with dose reduction, *PD* progression, *DO* drop-out

their treatment stopped, whilst patients in remission with or without dose reduction receive another course of the same chemotherapy until progression. The number of patients who move from one clinical state to another, or from one cycle to another, was quantified using a probability theory of transitions calculated from data in the literature. A cost of treatment and a dichotomous criterion of results, which has a value of 1 in survivors or survivors without relapse and 0 in the case of death or progression, are associated with each clinical state into which the patient moves. At the end of simulation, the total costs can be used to calculate and compare the annual follow-up costs per patient for the community of each of these 13 therapeutic options.

Allocating costs

The costs of chemotherapy delivery in hospital (in-patient), outpatient and ambulatory care and possible adverse events, have been estimated using NHS reference sources, although the calculation of expenditure has been limited to provision of medical care and consumption of medical products only. The UK costs were sourced by Fourth Hurdle Consulting Ltd (London, UK). Transfer payments, direct non-medical costs, and indirect costs were excluded from the scope of the analysis.

- Acquisition costs for IV agents were available from the British National Formulary 47 [20]. At the time of modelling, oral VNB was not commercially available in the UK, but a representative cost of £2.199 per milligram was applied (based on a price in several European countries of 3.1 € /mg).
- A cost for preparation/administration of anti-emetics, assumed identical for each therapeutic option was not applied. In the case of self-administration of the oral agent at home, a cost for pre-therapy counselling has been included [21, 22].
- Each agent is associated with one or more modes of administration: taxanes are administered during a day-time hospitalisation, whereas IV gemcitabine and VNB could be administered during a day-time hospitalisation or an outpatient visit on day 8, oral VNB could be administered during an outpatient visit or self-administered at home on day 8 following a visit to a GP for a blood test—day-time [21–23]. The cost of a day-time hospitalisation has been estimated at £354. The cost of a medical oncology outpatient visit has been estimated as £120. For a self-administered dose at home, the cost of a GP carrying out a local blood test (£20) and a pre-chemotherapy

counselling session with a hospital nurse (£15) are applied.
- A transport cost for each patient journey by hospital transport has been taken from Netten and Curtis [21, 22]. The costs of hospitalisation and transportation to and from hospital were added to the chemotherapy acquisition cost, assuming a body surface area of 1.7 m^2. The cost of administration of chemotherapies in different settings is shown in Table 3.
- Costs of managing specific grade 3 and 4 toxicities were taken from a number of publications [16–19], converted to UK costs (according to Purchasing Power Parity) and updated to 2003 prices. The main cost-incurring toxicities, based on occurrence in single-agent clinical studies, were febrile neutropenia, thrombocytopenia requiring blood transfusion, and nausea and vomiting. The costs of managing neurotoxicity and local reactions were not included. The costs of the four major groups of non-cumulative severe toxicity, were estimated for IV VNB, oral VNB, gemcitabine, docetaxel, and paclitaxel at £182, £239, £149, £138, and £125, respectively.

Results

Cost-minimisation study

The 13 possible regimens were evaluated based on the first option for drug administration: IV gemcitabine or VNB are administered alternatively during a day-time hospitalisation and an outpatient visit, the taxanes are administered during a day-time hospitalisation, and oral VNB is administered alternatively during an outpatient visit and self-administered at home following a visit to a GP for a blood test.

At the end of the 52 weeks simulation (Table 4):

- Oral VNB appears as the least expensive treatment: at a dose of 60 mg/m^2, with an alternating outpatient visit and home administration, its annual follow-up cost is £2,888.
- With dose escalation the cost is £3,449 (differential of £561).
- IV VNB at 25 and 30 mg/m^2/week has a cost of annual follow-up of £3,746 (differential of £687) and £3,986 (differential of £1,097), respectively.

Table 3 Costs of chemotherapy administration in hospital and during ambulatory care ($£_{2004}$)

Drug	Oral vinorelbine		IV vinorelbine		IV gemcitabine		IV docetaxel	IV paclitaxel	
Dose (mg/m^2)	60	80	25	30	1,000	1,250	100	175	200
Inpatient day	–	–	£585	£616	£731	£796	£1,763	£1,560	£1,810
Outpatient visit	£424	£512	£351	£382	£497	£562	£1,529	£1,326	£1,575
Home care	£285	£373	–	–	–	–	–	–	–

Table 4 Cost-minimisation study—results of the 52 weeks' simulation. *VNB* Vinorelbine

Therapeutic options	Cost minimisation[a]		Sensitivity analysis[b]	
	Cost ($£_{2004}$)	Incremental cost	Cost ($£_{2004}$)	Incremental cost
Oral VNB, 60 mg/m^2, D1–D8	2,888		3,448	
Oral VNB, D1–D8, 60–80 mg/m^2	3,449	+561	4,009	+561
IV VNB, 25 mg/m^2, D1–D8	3,746	+858	4,688	+1,240
Oral VNB, 60 mg/m^2/week	3,889	+1,001	4,938	+1,490
IV VNB, 30 mg/m^2, D1–D8	3,986	+1,097	4,928	+1,480
Oral VNB, 60–80 mg/m^2/week	4,682	+1,793	5,731	+2,283
IV VNB, 25 mg/m^2/week	4,980	+2,092	6,746	+3,298
Gemcitabine, 1,000 mg/m^2, D1–D15	5,081	+2,193	6,458	+3,010
IV VNB, 30 mg/m^2/week	5,327	+2,439	7,093	+3,645
Gemcitabine, 1,250 mg/m^2, D1–D8	5,332	+2,444	6,274	+2,826
Paclitaxel, 175 mg/m^2	5,977	+3,088	5,977	+2,529
Docetaxel, 100 mg/m^2	6,766	+3,878	6,766	+3,318
Paclitaxel, 200 mg/m^2	6,897	+4,009	6,897	+3,449

[a] On day 8—outpatient visits for IV VNB and gemcitabine, home administration of oral VNB

[b] Day-time hospitalisations for IV VNB and gemcitabine, outpatient visits administration of oral VNB

– Using a days 1 and 8 every 3 weeks schedule, the above four VNB scenarii have costs over 1 year of follow-up of £3,889, £4,682, £4,980, and £5,327, respectively.
– Gemcitabine at 1,250 mg/m^2 in days 1, 8, and 15 every 4 weeks, docetaxel at 100 mg/m^2 every 3 weeks and paclitaxel at a dose of 175 and 200 mg/m^2 every 3 weeks, incurred annual follow-up costs of £5,081, £5,332, £6,766, £5,977, and £6,897, respectively.
– Oral VNB allows savings per patient managed for 1 year of £2,193 to £2,444 compared to gemcitabine, and of £3,088 to £4,009 compared to taxanes.

Sensitivity analysis

In the sensitivity analysis, the two other options on schedules and administration strategies were tested.

1. IV gemcitabine or VNB are administered alternatively during a day-time hospitalisation and an outpatient visit, the taxanes are administered during a day-time hospitalisation, and oral VNB is administered during an outpatient visit.
2. IV chemotherapies are administered during a day-time hospitalisation, oral VNB is administered during an outpatient visit (Table 4).

The results showed:

- Whatever the place of administration of the chemotherapies, oral VNB remains the least expensive option. If every oral VNB administration at a dose of 60 mg/m^2 is carried out in an outpatient setting, the annual cost per patient is £3,488. For a weekly schedule with dose escalating from 60 to 80 mg m^{-2} week^{-1}, the cost rose to £4,009.
- IV VNB administrated during a day-hospitalisation at a dose of 25 and 30 m^{-2} week^{-1} had a cost of annual follow-up of £4,688 and £4,928, respectively. Using a days 1 and 8 every 3 weeks schedule, the above four VNB scenarii have costs over 1 year of follow-up of £4,938, £5,731, £6,746, and £7,093, respectively.
- Gemcitabine at 1,250 mg/m^2 on days 1, 8, and 15 every 4 weeks, docetaxel at 100 mg/m^2 every 3 weeks and paclitaxel at 175 and 200 mg/m^2 every 3 weeks, incurred annual follow-up costs of £6,274, £6,458, £6,766, £5,977, and £6,897, respectively.
- Oral VNB administered in hospital allows savings of £2,826 to £3,010 compared to gemcitabine administrated in a day-hospitalisation, and of £1,633 to £1,884 compared to gemcitabine administrated alternatively in a day-hospitalisation and an outpatient visit. Compared to taxanes, the oral form at hospital allows savings of £3,318 to £3,645 per patient managed for 1 year.

In order to check the validity of these results, we explored the realm of the possible. The cost of toxicities were changed using multiplication coefficients varying between 1 and 10. This allowed checking of which cost increases or reductions would be likely to challenge the therapeutic options of equivalent effectiveness. If the cost of toxicities (i.e. the rates of each toxicity multiplied by the average costs of managing the toxicity reaction) is multiplied by a coefficient equal to 4.3, oral VNB appears, whatever the form of management used (outpatient/GP visit), remained the least expensive option. For an equivalent cost between gemcitabine and the weekly oral form, the cost of toxicities must be multiplied by 4.4.

Discussion

This study compared NICE recommended third-generation agents used as monotherapy in NSCLC. In randomised trials, the third-generation regimens show comparable efficacy to one another, but a better response rate and time to progression, and improved tolerability compared to older treatments. In patients who are not suitable for platinum-based therapy, monotherapy has been shown to extend survival, even in elderly patients [26]. Thirteen treatment schedules were identified by oncology experts. The flexibility of administration for oral VNB offers several options for the d8 dose. Indeed, although home administration with a GP/local hospital blood test on d7 was considered a feasible option, some clinicians wanted to see their patients on d8, to maintain adequate awareness of performance status and tolerance to treatment. Where the patient presents on d8 at the chemotherapy day care unit, patients will be seen by the clinician or by a nurse. The prescription may be taken in front of the nurse in the chemotherapy unit, or at home.

A synthesis [1, 2] was conducted to identify economic studies or costing papers previously conducted on the use of paclitaxel, docetaxel, gemcitabine, and VNB for the treatment of NSCLC: seven studies considered gemcitabine, five considered VNB, one included both gemcitabine and VNB regimens, and two considered paclitaxel only. None of the economic or costing studies considered docetaxel. The economic evaluations are predominantly from a United States or

Canadian perspective. No United Kingdom economic evaluations were identified. A series of pairwise comparisons of the drugs from actual published trials could be found; in the majority of cases the comparator is the best supportive care (BSC), which implies treatment that aims to relieve symptoms but that does not attempt to prolong life. We might suppose also that less intensive hospital management and the reduction in adverse events would increase the comfort of patients who stay in their normal life environment, and of the family helpers, but no significant difference in quality of life between treatment arms has been demonstrated despite a lower toxicity rate. The costs of VNB, gemcitabine, and taxanes and their adverse events have been estimated in our analysis using the references of the UK NHS. Most of these other studies did not include the cost of managing adverse events or, in some cases, the cost of chemotherapy, and all excluded non-health service costs.

The most recent study (Berthelot et al. [27]) considered gemcitabine, VNB, and paclitaxel as monotherapy and in combination with platinum salts. VNB is standard treatment in Canada and has been reported to deliver cost savings or low incremental costs compared with BSC alone. Gemcitabine and paclitaxel also have small but acceptable incremental costs over BSC (Can$2,200 and Can$3,775, respectively). Berthelot determined that gemcitabine had an incremental cost per life-year saved (LYS) of Can$17,400 compared with VNB and of Can$6,800 compared with BSC. In another Canadian study comparing paclitaxel with BSC, Earle and Evans [28] found an incremental cost of Can$3,375 and an ICER per LYS of Can$4,778. Smith et al. [29] and Hillner and Smith [30] reported VNB in combination with cisplatin as having an ICER of $17,700 per LYS compared to single-agent VNB. In further comparisons using BSC as the base case, VNB and VNB–cisplatin were cost-saving when administered on an outpatient basis and incurred an incremental cost on an inpatient basis.

Conclusion

Lung cancer is the most common form of cancer in England and Wales, and is the cause of approximately 22% of cancer-related deaths each year (with 33,600 deaths in 2002) [24]. Despite this, lung cancer does not always receive the policy attention accorded to other types of cancer, such as breast and colorectal. However, the publication of the UK NHS Plan for Cancer [25] in September 2000 highlighted the government's commitment to invest in cancer services as anational priority. Given that NICE guidance in 2001 concluded that there was no significant difference in clinical effectiveness between any of the third-generation agents available for the treatment of advanced NSCLC, the question faced by the NHS is which interventions are most cost-minimising in implementing this plan? This study has demonstrated that VNB appears as the most cost-minimising therapeutic option. Additionally, the oral formulation allows cost savings attributable mainly to the reduction in hospital resource utilisation provided by self-administration at home. Sensitivity analyses confirmed the superior cost savings with oral VNB. On this basis, the oral form was endorsed by the Scottish Medicines Consortium in June 2005 as first-choice treatment within NHS Scotland for the treatment of advanced NSCLC.

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