Vinflunine is a vinca alkaloid licensed in the UK for the treatment of adults with advanced or metastatic TCC of the urothelial tract after failure of a prior platinum-containing regimen. The approval was based on a Phase III study comparing vinflunine (n=253) to best supportive care (BSC; n=117), with overall survival (OS) as the primary endpoint. The difference in OS (median of 6.9 months with vinflunine versus 4.6 months with BSC) was not statistically significant for the intention-to-treat (ITT) population (HR 0.88; 95% CI 0.69 to 1.12), however results for a multivariate analysis that adjusted for prognostic factors did achieve statistical significance (HR 0.77; 95% CI 0.61 to 0.98). A post-hoc analysis excluding 13 patients that were found to have violated the protocol (the ‘eligible ITT population’) resulted in a lower OS for BSC and the difference was statistically significant (6.9 months versus 4.3 months; HR 0.78; 95% CI 0.61 to 0.99).

Since there is no standard second-line therapy, the study included BSC as a comparator. In clinical practice, other agents are used outside their licence for a small proportion of suitable patients, but their relative efficacy compared with vinflunine is unknown.

NICE does not recommend vinflunine for use within its licensed indication. The Appraisal Committee was not persuaded that the evidence of effectiveness would be generalisable to the whole population who might receive vinflunine in UK clinical practice compared with BSC – as the population in the study was younger, fitter and had better renal function than the general UK population with this disease, and the study excluded patients who had previously received neoadjuvant or adjuvant chemotherapy (commonly used in the UK). In addition the trial population were considered to have a poor prognosis, whereas the license of vinflunine covers treatment of all patients, regardless of prognosis.

As well as querying the generalisability of the Phase III data, the Appraisal Committee concluded that the extent of the clinical effectiveness of vinflunine compared with BSC had not been conclusively demonstrated. The results from the ITT population were considered to be the most appropriate as randomisation had not been broken – and the difference in OS between the study arms in this population was not statistically significant. Additionally it was not considered to be a cost-effective use of NHS resources (the most plausible ICER was above £120,000 per QALY gained).

Vinflunine is associated with a relatively high incidence of serious adverse events such as neutropenia (grade 3 or 4 events seen in 50% of patients in clinical trials) and concurrent use of growth factors and prophylactic antibiotics may often be required in practice. The use of laxatives and dietary measures is recommended from day 1 to day 5 or 7 after each vinflunine administration in order to prevent constipation (grade 3 or 4 events seen in 16% of patients receiving vinflunine).
Background

Vinflunine

Vinflunine (Javlor®) is a vinca alkaloid licensed in the UK for use as monotherapy for the treatment of adult patients with advanced or metastatic transitional cell carcinoma (TCC) of the urothelial tract after failure of a prior platinum-containing regimen. Its approval for this indication was based on one randomised, open-label phase III study comparing vinflunine to best supportive care (BSC), and supported by two single-arm phase II trials (1). Vinflunine is currently the only treatment specifically licensed in the UK for the second line treatment of advanced or metastatic TCC.

Disease background

TCC is the most common type of bladder cancer, and is most frequently seen in people aged 65 years and over. Most are papillary carcinomas which are superficial and well-differentiated, but some are sessile tumours which are more insidious, invade early, and metastasise (2).

Patients with advanced TCC that has invaded the bladder wall or spread to the lymph nodes may receive treatment with surgery (radical cystectomy) and/or radiotherapy. Chemotherapy may be given with or without radiotherapy in the neoadjuvant or adjuvant setting, in an attempt to improve cure rates. If the cancer is too advanced for surgery/radiotherapy or has recurred after these treatments, chemotherapy can be used to improve quality of life and survival. Platinum-based regimens are most commonly used in the first-line treatment in this setting (usually cisplatin or carboplatin plus gemcitabine) (2).

The life expectancy of patients with advanced or metastatic TCC of the urothelial tract whose disease has progressed after first-line chemotherapy is usually less than 6 months. There is currently no standard treatment for this patient group, although a number of agents may be used for those who are fit enough to receive further treatment (3).

Clinical guidelines on bladder cancer

A number of clinical guidelines on advanced/metastatic bladder cancer are available. All discuss platinum-based chemotherapy (mainly gemcitabine-cisplatin) as the standard first-line treatment, and note that the data for second-line treatments are highly variable (vinflunine has the highest level of evidence in this setting to date).

Guidelines from the European Association of Urology (EAU) recommend that a trial of vinflunine be offered to patients progressing after platinum-based combination chemotherapy for metastatic disease, and that any other treatment should take place in the context of clinical trials (4).

US guidelines from the National Comprehensive Cancer Network (NCCN) note that patients with metastatic disease should be re-evaluated after 2-3 cycles of chemotherapy, with continuation only in those whose disease has responded or remained stable. If no response is noted, a change in therapy is advised, taking into account the performance status, extent of disease, and prior therapy administered. Although no standard exists, available options for second-line chemotherapy include docetaxel, paclitaxel and gemcitabine monotherapy. The guidelines do not discuss vinflunine as this is not currently licensed in the US (5).

A European Society for Medical Oncology (ESMO) guideline on bladder cancer (2011) note that the following independent adverse prognostic factors for survival have recently been validated: performance status (PS) >0, haemoglobin level <10 g/dl, and the presence of liver metastases. The guidelines note that the only valid Phase III study in this setting, in patients progressing after a first-line platinum-containing regimen, is that for vinflunine. They comment that the results suggest modest activity with a favourable safety profile; the survival benefit was however only statistically significant in the eligible patient population (not in the intention-to-treat population). They say that vinflunine is the only drug in Europe to be approved in this setting; however ‘it is unclear whether other (unlicensed) agents used in this setting would have similar benefit’ (6).

NICE guidance

NICE issued final guidance on vinflunine in January 2013, which does not recommend its use within its licensed indication for the treatment of advanced or metastatic TCC of the urothelial tract that has progressed after treatment with platinum-based chemotherapy (3). The Appraisal Committee concluded that the extent of clinical effectiveness of vinflunine compared with BSC had not been conclusively demonstrated due to uncertainty of the overall survival results. Additionally it was not considered to be a cost-effective use of NHS resources (the most plausible ICER was above £120,000 per QALY gained).
Epidemiology

The incidence of bladder cancer in England is approximately 8,800 per year, and bladder cancer accounts for 90% of cases of TCC of the urothelial tract. Therefore the incidence of TCC of the urothelial tract in England can be estimated at 9,800 per year (approximately 18 per 100,000 people) (7).

If it assumed that 30% of these patients have invasive or metastatic disease, 85% of these receive first-line chemotherapy, and 50% of these will be candidates for second-line treatment, the population who would be eligible for treatment with vinflunine can be estimated as around 2.2 per 100,000 people.

Published data

Efficacy

An open-label, randomised Phase III study (study 302) compared vinflunine (320mg/m² every 21 days) plus BSC (n=253) with BSC alone (n=117) in patients with advanced or metastatic TCC of the urothelial tract whose disease had progressed after at least two cycles of first-line platinum-based chemotherapy (or at least one cycle if there was clear evidence of progression at this stage) (3, 8). Participants had an ECOG PS of 0 or 1 and an estimated life expectancy of at least 12 weeks. Those who had received neoadjuvant or adjuvant chemotherapy were excluded. The median age of study participants was 64 years, 79% were male, and the majority of baseline characteristics were similar across the two treatment arms (although more patients in the vinflunine arm had received carboplatin as their first-line platinum treatment).

The primary outcome was median overall survival (OS) assessed in the intention-to-treat (ITT) population. This was 6.9 months in the vinflunine group and 4.6 months in the BSC group, respectively (hazard ratio [HR] 0.88; 95% CI 0.69 to 1.12). Although a median survival benefit of 2 months was achieved as hypothesised, the difference did not reach statistical significance. Results for the pre-specified, multivariate Cox analysis, which adjusted for prognostic factors (performance status, visceral invasion, alkaline phosphatase, haemoglobin and prior pelvic irradiation), did achieve statistical significance between the treatment groups in the ITT population: HR 0.77 (95% CI 0.61 to 0.98).

Results were also presented for the ‘eligible ITT population’, which excluded 13 patients (4 patients in the vinflunine arm and 9 in the BSC arm) who were found (upon retrospective review) to have clinically significant protocol violations (mainly no disease progression or use of neoadjuvant or adjuvant chemotherapy). A post hoc analysis excluding these patients found a statistically significant survival benefit with vinflunine, with a median OS of 6.9 months and 4.3 months respectively (HR 0.78; 95% CI 0.61 to 0.99; p=0.0403). An extended multivariate analysis was also done, adjusting for the same prognostic factors outlined above plus additional baseline characteristics such as age, sex and disease stage at diagnosis. This analysis also showed a statistically significant overall survival benefit for vinflunine (HR 0.68, 95% CI 0.52 to 0.88, p=0.0035).

[Note: Updated survival results after a median follow-up of 21 months were reported at conference and these were consistent with the previously reported results (9)].

Other results reported include the following:

- Progression-free survival (ITT population) was 3.0 months in the vinflunine arm and 1.5 months in the best supportive care arm (HR 0.68, 95% CI 0.54 to 0.86, p=0.0012).
- In the vinflunine arm, 46.5% of patients had stable disease after second-line treatment, 44.9% had progressive disease, and 8.6% had a partial or complete response. In the BSC arm, 27% of patients had stable disease, 73% had progressive disease, and none had a partial or complete response.
- After disease progression, palliative chemotherapy was used in 29% of patients in the vinflunine arm and 34% in the BSC arm; 60% of these re-treated patients received multi-agent chemotherapy.
- There were no statistically significant differences in overall EORTC QLQ-C30 global health status score between the two arms (p=0.658).

NICE TA: Discussion of the evidence

The Appraisal Committee and the clinical experts consulted during the guidance process noted the following points regarding the evidence (3):

- As there are no proven standard agents for second-line chemotherapy, BSC was the appropriate comparator for vinflunine.
- The population of the Phase III study was younger, fitter and had better renal function than the general population of UK patients with advanced or metastatic TCC of the urothelial tract.
- Patients who had received prior neoadjuvant or adjuvant chemotherapy were excluded from the study. Many patients in the UK who are eligible to receive second-line palliative chemotherapy will have received such treatment.
The manufacturer considered the trial population to be only people with a poor prognosis, based on a high proportion (74%) having visceral involvement, and the fact that it is unlikely that people with a better prognosis would be willing to be randomised to a trial in which one of the treatment options was BSC. No data were available for people in the whole licensed population for vinflunine with a better prognosis than the trial population.

Considering the above issues, the Appraisal Committee was not persuaded that the evidence of effectiveness would be generalisable to the whole population who might receive vinflunine in UK clinical practice compared with BSC. The Committee considered that the results from the ITT population were the most appropriate basis for its deliberations because randomisation had not been broken – in this analysis the difference in OS between the study arms was not statistically significant. It concluded that the extent of the clinical effectiveness of vinflunine compared with BSC had not been conclusively demonstrated. As the Committee was not persuaded that an extension to life of at least 3 months had been proven, the end-of-life advice did not apply to this appraisal.

Safety
The most common adverse events (any grade) associated with vinflunine across the Phase III study and the two Phase II studies also considered by NICE during the appraisal included constipation (55%), nausea (41%), infusion-site reactions (28%), stomatitis/mucositis (27%) and vomiting (27%). Overall, there were 6 deaths related to treatment (1.3%), of which 4 were a result of myelotoxicity. Four treatment-related deaths occurred in the vinflunine arm of study 302. Grade 3 or 4 toxicities relating to neutropenia, anaemia and constipation occurred in 50%, 19% and 16% respectively of patients in the vinflunine arm of study 302, compared with 1%, 8% and 1% of patients respectively in the BSC arm. Febrile neutropenia occurred in 6% of patients receiving vinflunine (none in the BSC arm) (3).

The Committee concluded that there were concerns about the tolerability of vinflunine, as the safety profile of second-line chemotherapy in this setting needed to be predictable, acceptable to patients and manageable (3).

Cost
Vinflunine is available in 50mg and 250mg vials, costing £212.50 and £1062.50 respectively (excluding VAT) (10). Assuming an average of 4.2 cycles, a dose of 287 mg/m² and a body surface area of 1.85 m² (these are all mean values taken from study 302), the following costs can be estimated:

- Average dose per cycle: 287 mg/m² x 1.85 m² = 530 mg
- Average cost per cycle (including 20% VAT): 2x250mg vials and 1x50mg vial (assuming wastage) = £2,805
- Average cost per patient for a total course of treatment = £2,805 x 4.2 cycles = £11,781

Based on these assumptions, and on an eligible population of 2.2 per 100,000 people (see epidemiology section), then use of vinflunine in this indication would be associated with an estimated cost of approximately £25,920 per 100,000 people per year.

Please note that costs may vary in different settings because of negotiated procurement discounts. In addition there will be other costs associated with treatment, including administration for intravenous infusion every 21 days in an outpatient setting, complete blood count before drug administration, constipation prophylaxis, and the treatment of adverse events.

The NICE Appraisal Committee considered the most plausible ICER to be above £120,000 per QALY gained. It further considered that additional uncertainties around the costs of adverse events and the modelling of survival data would increase the ICER.

Service implications
Although a number of agents have been used in the second-line setting, there are limited data and no agreed standard in current practice. If the comparator considered is BSC then the use of vinflunine will be associated with increased resource use, due to the need for intravenous infusion every 21 days (this will be in an outpatient setting). Vinflunine is associated with a relatively high incidence of serious adverse events such as neutropenia (50% grade 3/4; 6% febrile) and concurrent use of growth factors and prophylactic antibiotics would often be required in practice (11).
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<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Incidence (number of patients per 100,000 eligible for treatment)</th>
<th>Average duration of treatment (taken from trial data)</th>
<th>Cost per month/cycle</th>
<th>Cost per 100,000 population per month/cycle</th>
<th>Cost per 100,000 for average treatment duration</th>
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<td>Vinflunine</td>
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<td>£6,170</td>
<td>£25,920</td>
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References

4. European Association of Urology

Details of search strategy:

EMBASE: exp VINFLUNINE/ AND [exp *TRANSITIONAL CELL CARCINOMA/ OR exp *UROGENITAL TRACT CANCER/]
MEDLINE: vinflunine.af AND [exp *CARCINOMA, TRANSITIONAL CELL/ OR exp *UROLOGIC NEOPLASMS/]


The document reflects the views of LCNDG and may not reflect those of the reviewers

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