pegylated liposomal doxorubicin, 2mg/ml concentrate for solution for infusion (Caelyx®) No. (503/08)
Schering Plough

05 September 2008

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

pegylated liposomal doxorubicin (Caelyx®) is not recommended for use within NHS Scotland in combination with bortezomib for the treatment of progressive multiple myeloma in patients who have received at least one prior therapy and who have already undergone or are unsuitable for bone marrow transplant.

Results from an interim analysis showed that pegylated liposomal doxorubicin plus bortezomib significantly increased the time to progression compared to bortezomib monotherapy. At the time of the interim analysis only 31% of patients in the combination arm had reached the primary endpoint.

The manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Pegylated liposomal doxorubicin in combination with bortezomib for the treatment of progressive multiple myeloma in patients who have received at least one prior therapy and who have already undergone or are unsuitable for bone marrow transplant.

Dosing information

Pegylated liposomal doxorubicin 30 mg/m² as a one hour intravenous (iv) infusion on day four plus bortezomib 1.3 mg/m² as an IV bolus on days 1, 4, 8, and 11. Regimen repeated every three weeks.

The dose should be repeated as long as patients respond satisfactorily and tolerate treatment. Day four dosing of both medicinal products may be delayed up to 48 hours as medically necessary. Doses of bortezomib should be at least 72 hours apart.

Product availability date

September 2008

Summary of evidence on comparative efficacy

Doxorubicin, a cytotoxic anthracycline antibiotic, has a number of mechanisms of action, including the formation of covalent topoisomerase-DNA complexes, interference with the function of topoisomerase II, acting as a DNA intercalator, and generation of free radical intermediates. Bortezomib is a reversible inhibitor of the 26S proteasome which prevents targeted proteolysis and affects signaling cascades. This inhibition is thought to interfere with the mechanisms malignant cells use to inhibit the effect of chemotherapy, thus helping overcome chemo-resistance. Preclinical studies suggest bortezomib may enhance the activity of doxorubicin.

In a randomised open label study, 646 patients with multiple myeloma, whose disease had progressed after at least one prior therapy or was refractory to initial treatment, were assigned to either combination therapy with bortezomib 1.3 mg/m² iv bolus on days 1, 4, 8, and 11 plus pegylated liposomal doxorubicin 30 mg/m² iv infusion on day 4 given every three weeks (n=324) or monotherapy with bortezomib 1.3 mg/m² on days 1, 4, 8, and 11 every three weeks (n=322). Randomisation was stratified by β_2-microglobulin level ($\leq$2.5 mg/L, >2.5 mg/L and $\leq$5.5 mg/L and >5.5 mg/L).

The primary endpoint was the time to progression (TTP), defined as the interval between the date of randomisation and the date of disease progression or death due to progression in the intention to treat (ITT) population. The median TTP was estimated using a Kaplan-Meier plot, and a 95% confidence interval (CI) was computed. Subjects who died without documented disease progression were censored at the date of their last evaluation. Secondary endpoints included overall survival estimated using the Kaplan-Meier method. An interim analysis and final analysis were planned when 230 and 460 events were observed. The TTP efficacy statistical boundary was set at p=0.003 and p=0.048, for the interim and final analyses, respectively. Patients were treated with permitted supportive therapy as necessary. Treatment continued until disease progression, or unacceptable treatment-related toxicity, up to a total of 8 cycles. Dose adjustments were permitted.

The interim analysis was performed after 249 events with a median follow up of 3.9 months, a median of five cycles received and median duration of treatment of approximately 105

days. At the interim analysis, 47% (150/322) of patients in the bortezomib arm and 31% (99/324) of patients in the pegylated liposomal doxorubicin/bortezomib arm had progressed or died. The primary outcome, median TTP was significantly longer with pegylated liposomal doxorubicin/bortezomib treatment (9.3 months) than with bortezomib monotherapy (6.5 months), p=0.000004, exceeding the pre-specified statistical boundary. This represented a 45% reduction in risk of progression in patients treated with the combination. The hazard ratio (HR) for the difference between treatments was 1.82 (95% CI: 1.41 to 2.35). Subgroup analysis showed pegylated liposomal doxorubicin/bortezomib significantly improved TTP, regardless of the patient's baseline characteristics, compared to bortezomib monotherapy. As the statistical boundary for the primary endpoint was achieved by the interim analysis a study amendment allowed patients treated with bortezomib alone to crossover to the combination therapy arm.

The Food and Drugs Administration (FDA) requested further analyses of TTP and OS. After another six months of follow up and at 407 events (184 (57%) in the pegylated liposomal doxorubicin /bortezomib arm and 223 (69%) in the bortezomib arm), the median TTP was 8.9 months in the pegylated liposomal doxorubicin/bortezomib arm and 6.9 months in the bortezomib arm, p=0.000013; HR 1.55 (95% CI: 1.27 to 1.89).

At the interim analysis, 28 (9%) patients in the combination therapy and 39 (12%) in the monotherapy group had died, representing a 32% reduction in risk of death for patients treated with pegylated liposomal doxorubicin/bortezomib; HR 1.48 (95% CI: 0.91 to 2.41). At the FDA requested analysis at a median follow up of 11 months, 58 (18%) patients in the pegylated liposomal doxorubicin/bortezomib arm and 81 (25%) in the bortezomib arm had died, a 29% risk reduction of death; HR 1.41 (95% CI:1.0 to 1.97). Subsequently, the Committee for Medical Products for Human Use (CHMP) requested a further additional analysis of OS. With a median follow up of 18 months, there had been a further 67 deaths, 38 (total = 96 (30%)) in the combination arm and 29 (total = 110 (34%)) in the bortezomib arm, giving a 14% reduction in the risk of death.

Summary of evidence on comparative safety

The adverse events observed with the pegylated liposomal doxorubicin/bortezomib combination were consistent with the known safety profiles of both agents. No unexpected safety concerns were observed.

The incidence of serious adverse events was similar in the two treatment groups. However, in the combination arm grade 3 or 4 adverse events were more frequent (80% vs. 64%). In addition, neutropenia (all grades: 35% vs. 20% and grade 3/4: 29% vs. 15%) and stomatitis were more frequent (all grades: 18% vs. 3%) in the combination arm. Hand-foot syndrome only occurred in the combination group (16%) and led to discontinuation of pegylated liposomal doxorubicin in 5% of patients. The incidence of all cardiac adverse events was low and similar between the two treatment groups.

The number of patients who withdrew from the study due to adverse events was 66/322 (20%) in the bortezomib group and 86/234 (27%) in the pegylated liposomal doxorubicin/bortezomib group.

Summary of clinical effectiveness issues

Results from an interim analysis showed, pegylated liposomal doxorubicin/bortezomib combination therapy significantly improved TTP compared with bortezomib monotherapy in patients with multiple myeloma who had received at least one prior therapy and who had already undergone or were unsuitable for bone marrow transplant. The study was terminated when only 31% of patients in the combination arm had reached the primary endpoint and consequently the FDA requested a further analysis after another six months of follow up. In this analysis, 57% of patients in the combination arm had reached the primary endpoint and these results also showed a significant advantage for the combination therapy despite cross-over from the monotherapy arm.

The more clinically relevant outcome of OS, a secondary outcome in the study, was estimated using a Kaplan Meier plot. At the interim analysis only a small percentage of patients had died. The OS results at 18 months follow up were confounded by the termination of the study, the cross-over of patients and the 65% of patients who had progressed and were treated with subsequent therapies. The reduction of risk of death when treated with the combination therapy fell from 32% at a median of 3.9 months follow up (interim analysis), to 29% at 11 months follow up (FDA analysis) and to 14% at 18 months follow up (CHMP analysis). Only at the time of the FDA analysis did the benefit in mortality approach significance. The CHMP concluded that: “while a benefit on overall survival cannot be considered to have definitively been established, it is strongly suggested, and there is certainly no suggestion of a detrimental effect. The Kaplan-Meier curves show separation of the curves, favouring the combination therapy”.

There are a number of issues that might affect the generalisability of the results to the Scottish population. The comparator, bortezomib, used in the study may not reflect Scottish practice for the treatment of multiple myeloma at first relapse due to recent SMC decisions. Current treatments in multiple myeloma are varied with the use of both unlicensed and off-label drugs and combinations, and therefore the place of the pegylated liposomal doxorubicin/bortezomib combination in practice is difficult to assess. The patient population in the study was young for this indication, with the overall median age 61 years. The median age presenting with multiple myeloma is estimated to be 70 years. They were also a fit population with Eastern Cooperative Oncology Group (ECOG) performance status of either 0 (44%) or 1(56%).

The open nature of the study may have biased the reporting of adverse event rates and possibly response rates and although quality of life data was recorded (although not yet reported) due to the open study design its usefulness is expected to be limited.

Summary of comparative health economic evidence

The manufacturer provided a cost-utility analysis comparing bortezomib in combination with pegylated liposomal doxorubicin to treatment with bortezomib monotherapy and high dose dexamethasone (HDD). The patient population had progressive multiple myeloma (MM) and had received at least one prior therapy and had already undergone or were unsuitable for bone marrow transplant. The base case time horizon was ten years.

The manufacturer used a Markov model, with a simple but adequate structure with the three states of progression-free, progression, and dead. Clinical data came from relevant clinical studies and the methods used to estimate survival beyond the study periods were

acceptable. The mean survival for the combination arm was 4.86 years, compared to 3.89 years for monotherapy, and 3.24 years for HDD. There were limitations in data used to model adverse events, resource use and utility values but the sensitivity analyses showed these were not major factors in terms of the results.

The combination therapy had an incremental cost effectiveness ratio of £17,303 per QALY compared to bortezomib alone and £27,880 compared to HDD.

The results were sensitive to dose-related costs, survival rates and time horizon. With a mean of six cycles of bortezomib and a £100 administration cost per dose in the monotherapy and combination arms of bortezomib, the ICERs were £19,017 and £32,157 respectively. (Note these assumptions are consistent with the dose regimens and costs used in the recent NICE Single Technology Appraisal of bortezomib monotherapy.) In the clinical study, the mean number of cycles was 5.3; no clinical benefit was attributed to assumed additional therapy. With a five year time horizon the ICERs were £26,303 and £46,181 respectively. Applying the lower 95% confidence interval for overall survival in the combination arm resulted in bortezomib dominating the combination therapy and gave an ICER of £70,872 for combination therapy compared to HDD therapy. Using the upper 95% confidence interval for overall survival in the combination arm gave ICERs of £12,988 and £20,582 for the combination therapy compared to bortezomib monotherapy and HDD therapy respectively. Using the clinical data from the FDA analysis gave an ICER of £24,070 for bortezomib combination compared to monotherapy and £42,648 versus HDD. However these ratios are difficult to interpret because of the high cross-over from the bortezomib monotherapy arm.

The key issues are:

The choice of bortezomib monotherapy as a comparator may not have been appropriate given recent SMC decisions and treatment patterns in Scotland

- Patients in the clinical studies had a mean age of 61 and were generally fitter than might be expected of similar patients in Scotland who are generally older when presenting for diagnosis. These differences suggest the survival benefit modelled may not generalise to the Scottish population.
- The considerable uncertainty on long term survival data because of the nature of the clinical study.

These factors suggest the base case is an underestimate of the likely cost per QALY and thus the drug is not recommended.

Summary of patient and public involvement

Patient Interest Group Submissions were received from:

- Leukaemia CARE
- Myeloma UK

Additional information: guidelines and protocols

Guidelines on the diagnosis and management of multiple myeloma 2005, published by the British Committee for Standards in Haematology (BCSH). These guidelines recommended that the most appropriate management must be determined on an individual basis depending on age, prior therapy and clinical condition.

Additional information: previous SMC advice

Following a full submission, SMC published advice in October 2004: Bortezomib (Velcade®) is accepted for use within NHS Scotland for the treatment of patients with multiple myeloma who have received at least two prior therapies, have demonstrated disease progression on the last therapy and who are refractory to alternative licensed treatments for this stage of the disease. Bortezomib produced a disease response in approximately one third of these patients in an open-label uncontrolled study. Any other use of bortezemib should only take place within the context of a controlled study. The manufacturers are encouraged to mount an observational study in collaboration with haemato-oncologists to gain more information on the benefits and risks of this therapy.

Following a resubmission SMC published advice in August 2007: Bortezomib (Velcade®) is not recommended for use within NHS Scotland as mono-therapy for the treatment of progressive multiple myeloma in patients who have received at least one prior therapy and who have already undergone or are unsuitable for bone marrow transplantation. Bortezomib, compared to high dose dexamethasone, prolonged time to disease progression by 2.7 months and improved survival in patients who had progressive multiple myeloma despite previous treatment with one to three lines of therapy. However, the manufacturer's justification of the treatment's cost in relation to its health benefits was not sufficient to gain acceptance by SMC and they did not present a sufficiently robust economic analysis.

Following a full submission, SMC published advice in May 2008: Lenalidomide (Revlimid®) is not recommended for use within NHS Scotland in combination with dexamethasone for the treatment of multiple myeloma in patients who have received at least one prior therapy. Lenalidomide plus dexamethasone significantly increased the time to disease progression compared with dexamethasone alone in multiple myeloma patients who had been treated with at least one prior therapy. The manufacturer did not present a sufficiently robust case and in addition the manufacturer's justification of the treatment's cost in relation to its health benefits was not sufficient to gain acceptance by SMC. The licence holder has indicated their intention to resubmit.

Additional information: comparators

There are a variety of treatment options for patients who relapse after initial treatment. Choice of treatment is influenced by the age and performance status of the patient, length of response to previous therapy, relapse after response versus primary refractory disease and initial course of disease management.

Induction of remission with intensive chemotherapy such as CVAD (cyclophosphamide/ vincristine/doxorubicin/dexamethasone) is followed by consolidation with high dose melphalan then bone marrow transplant or less aggressive treatment with regimens such as oral melphalan plus prednisolone or cyclophosphamide. Bortezomib as monotherapy has been accepted for use by the SMC in patients who have received at least two prior therapies but not for patients who have received only one.

Cost of relevant comparators

Drug	Dose regimen	Length of cycle	Cost per cycle (£)
Pegylated liposomal doxorubicin Bortezomib	**30mg/m^2 iv on day 4 1.3mg/m^2 iv day 1, 4, 8, 11**	**21 days**	**4,188**
Lenalidomide Dexamethasone	25mg orally on days 1-21 40mg orally on days 1-4, 9-12, 17-20	28 days	4,388
Bortezomib	1.3mg/m^2 iv on days 1,4,8,11	21 days	3,050
Cyclophosphamide[A] Vincristine Doxorubicin Dexamethasone	500mg orally or iv on days 1,8,15 0.4mg iv days 1-4 9mg/m^2 iv days 1-4 40mg orally days 1-4 and 12-15	21 days	240 to 250
Vincristine[B] Doxorubicin Dexamethasone	0.4mg iv days 1-4 9mg/m^2 iv days 1-4 40mg orally days 1-4 and 12-15	21 days	235
Dexamethasone[C]	40mg orally days 1-4, 9-12, 17-20	28-35 days	21
Melphalan Prednisolone	7mg/m^2 orally days 1-4 40mg orally days 1-4	28 days	14
Cyclophosphamide	300-500mg/m^2 orally or iv weekly	21-28 days	5 to 20

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 2nd July 2008. iv=intravenous A = CVAD regimen; B = VAD; C = high dose dexamethasone; costs based on a body surface area of 1.8 m^2. Regimens based on Medical Research Council Myeloma IX protocol and advice from Scottish haemato-oncologists.

Additional information: budget impact

The manufacturer estimated bortezomib in combination with pegylated liposomal doxorubicin would displace HDD and have a net impact, to include resource savings, of £124k in year 1, rising to £322k in year 5. This assumed 336 new cases of multiple myeloma each year, of whom 85% (285) would be alive after the first year and 33% (94) of these eligible for second-line therapy. In year 1, 24 of such patients, rising to 69 patients in year 5 were assumed to be treated with bortezomib in combination with pegylated liposomal doxorubicin.

The assessor has estimated the potential impact on the drugs budget to be £500k in year 1, rising to £1.4m in year 5. This assumes the same patient numbers of 24 receiving combination therapy rather than HDD in year 1, rising to 69 in year 5 and with 5 cycles of treatment.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 15 August 2008.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted references were supplied with the submission.

Orlowski RZ, Nagler A, Sonneveld P et al Randomised phase lll study of pegylated liposomal doxorubin plus bortezomib compared with bortezomib alone in relapsed or refractory multiple myeloma:combination therapy improves time to progression. J Clin Oncol 2007:25;3892-3901

The European Medicines Agency (EMEA) European Public Assessment Report. Liposomal doxorubicin plus bortezomib (Caelyx® plus Velcade®). EMEA/H/C/000089/II/0045 http://www.emea.europa.eu/humandocs/PDFs/EPAR/Caelyx/AR-H-089-II-45.pdf