Pegylated liposomal doxorubicin hydrochloride for ovarian cancer

A systematic review and economic evaluation of pegylated liposomal doxorubicin hydrochloride for ovarian cancer

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Executive summary

Health Technology Assessment 2002; Vol. 6: No. 23

Health Technology Assessment
NHS R&D HTA Programme

Executive summary

Background

Ovarian cancer is the most common gynaecological cancer with an annual incidence of 21.6 per 100,000 in England and Wales. As the early stages of ovarian cancer are often asymptomatic, most cases are not detected until the advanced stages. Consequently, prognosis after diagnosis is poor with 5-year survival in the UK of only about 30%. Paclitaxel and platinum-based (cisplatin/carboplatin) therapy are currently recommended as first-line chemotherapy for ovarian cancer. However, most patients develop resistant or refractory disease eventually requiring second-line therapy. Patients may respond to re-challenge with platinum agents if the treatment-free interval is > 6 months, but an alternative is often required. Topotecan has recently been recommended as one agent to be considered for second-line therapy, and pegylated liposomal doxorubicin hydrochloride is one of three other drugs currently licensed in the UK for use in second-line therapy.

Aims of the review

To examine the clinical effectiveness and cost-effectiveness of intravenous pegylated liposomal doxorubicin hydrochloride (Caelyx®, Schering-Plough Ltd, UK; Doxil®, Alza Corporation, USA) as second-line treatment for advanced ovarian cancer after failure of first-line platinum-based therapy.

Methods

Search strategy

Twenty-three electronic databases, databases of ongoing research and Internet resources were searched from inception to June 2001, and bibliographies of retrieved articles and pharmaceutical company submissions were examined.

Inclusion/exclusion criteria

Two reviewers independently screened all titles/abstracts, and made final decisions to include/exclude studies based on full copies of articles. Any disagreements were resolved through discussion.

Only randomised controlled trials (RCTs) and full economic evaluations comparing pegylated liposomal doxorubicin hydrochloride to non-pegylated liposomal doxorubicin hydrochloride regimens or standard care were included. Only second-line therapy of advanced disease after failure of first-line platinum-based therapy was considered, and the outcomes included were survival, response, symptom relief, quality of life (QoL), adverse events and costs.

Data extraction and quality assessment

Data were extracted by one reviewer and checked by another. Two reviewers, using specified criteria, independently assessed the quality of the clinical effectiveness and economic studies. Any disagreements were resolved through discussion.

Analysis strategy

Due to the limited number of studies included in the review, the outcome data could not be pooled statistically. Clinical effectiveness data were discussed according to outcome. RCTs were discussed separately from Phase II studies. For time to event data, hazard ratios with 95% confidence intervals (CIs) were presented where available. For the remaining outcomes, relative risks were reported or calculated where appropriate and where sufficient data were available, and also presented as forest plots without pooled estimates. Economic data were presented as a summary and critique of the evidence. Additional analysis was undertaken to explore cost-effectiveness more fully, including assessment of assumptions underlying the submitted economic analyses using relevant experts, estimation of differential mean survival duration, presentation of cost-effectiveness acceptability curves, assessment of the sensitivity of cost-effectiveness to possible differences between therapies in health-related QoL (HRQoL) and estimation of the expected value of additional research.

Results

Included studies

Of 143 titles/abstracts screened for relevance, full copies of 53 articles were assessed for inclusion. ▶

Eighteen published papers of two RCTs and six Phase II studies of clinical effectiveness and two economic evaluations were included. Further details of one RCT, three Phase II studies and the economic evaluations were obtained from Schering-Plough Ltd. Overall, one international multicentre RCT comparing pegylated liposomal doxorubicin hydrochloride with topotecan (trial 30-49) was used in the final assessment of clinical effectiveness; and two cost-minimisation analyses based on trial 30-49 were used in the assessment of cost-effectiveness.

Quality of clinical effectiveness data

The RCT (trial 30-49) was of reasonably good quality, although valid intention-to-treat analyses were not used to assess outcome data. The six Phase II studies had several methodological problems and were of a much weaker design. Interpretation of such data requires great caution and the evidence from these studies was, therefore, not included in the final assessment of clinical effectiveness.

Quality of economic evaluations

Trial 30-49 on which both economic analyses were based was of reasonably good quality. The economic analyses used a cost-minimisation design, which was justified by the RCT being designed to show equivalence in overall survival. However, no equivalence in HRQoL was established. Other characteristics of the economic evaluations were generally of high quality.

Assessment of clinical effectiveness

The clinical effectiveness assessment was based on the best available evidence, although this was limited to data from trial 30-49 on 474 participants. Apart from some minor exceptions, there were no significant differences between pegylated liposomal doxorubicin hydrochloride and topotecan in overall survival, median survival, response rate, median time to response, median duration of response and QoL. The only significant differences reported were identified in subgroup analyses (platinum-sensitive disease and disease without ascites), which were of questionable validity, and their relevance to a general advanced ovarian cancer patient population undergoing second-line chemotherapy is unclear. However, significant differences were observed in the incidence of adverse events. Topotecan was associated with increased haematological toxicities (including neutropenia, leukopenia, anaemia and thrombocytopenia), alopecia, nausea and vomiting. Pegylated liposomal doxorubicin hydrochloride increased the incidence of palmar–plantar erythrodysesthesia, stomatitis, mucous membrane disorders and skin rashes.

Assessment of cost-effectiveness

The analysis of costs was thorough in both economic analyses. The company submission showed a mean cost saving from the use of pegylated liposomal doxorubicin hydrochloride of £2657. The mean cost with pegylated liposomal doxorubicin hydrochloride was £9970 (95% CI, £9080 to £10,861) compared with £12,627 (95% CI, £11,527 to £13,727) with topotecan. In the analysis by Smith and colleagues,[*] the mean saving was US$2909 (95% CI, $779 to $3415), approximately £2078, in favour of pegylated liposomal doxorubicin hydrochloride. In both cases, the savings were largely due to lower resource use in the management of adverse events with pegylated liposomal doxorubicin hydrochloride. The fairly extensive sensitivity analysis showed the estimates of differential costs were robust to changes in key parameter values. Further analysis for this report showed that when a full probabilistic cost-effectiveness analysis was undertaken and effectiveness expressed in terms of mean survival duration, there was a high probability that pegylated liposomal doxorubicin hydrochloride is more cost-effective (70–80%). However, the possible differences in HRQoL between the two therapies, reflecting differences in adverse events, may produce quite different cost-effectiveness results when effectiveness is expressed in terms of quality-adjusted life-years (QALYs) – a preferable measure when both length of life and QoL are potentially influenced. Therefore, although pegylated liposomal doxorubicin hydrochloride is very likely to have lower costs than topotecan, its overall cost-effectiveness is unclear.

Conclusions

The main results of this review suggested that there is little RCT evidence for assessment of the effectiveness of pegylated liposomal doxorubicin hydrochloride as second-line therapy for advanced ovarian cancer. Data from only one RCT was included in the final assessment of clinical effectiveness, and only two economic evaluations relevant to the UK NHS were identified and included in the cost-effectiveness assessment.

The evidence suggested that there were no differences between pegylated liposomal doxorubicin hydrochloride and topotecan in the main clinical outcomes. However, significant differences were ▶

observed in the incidence of adverse events. The clinical significance of these findings was not discussed. Overall, the clinical effects of pegylated liposomal doxorubicin hydrochloride could at best be described as modest, however, the only other comparator considered in this review offered no real advantages. If anything, pegylated liposomal doxorubicin hydrochloride offered possible clinical advantages over topotecan due to fewer adverse events.

Based on existing data, pegylated liposomal doxorubicin hydrochloride is less costly than topotecan. When effectiveness was based on survival duration, pegylated liposomal doxorubicin hydrochloride had a high probability of being cost-effective. However, differences between the two therapies are likely to exist in overall HRQoL, which, when expressed in terms of QALYs, could alter these cost-effectiveness results markedly.

Recommendations for research

To provide a clearer picture of clinical effectiveness, further good quality RCTs comparing pegylated liposomal doxorubicin hydrochloride with other licensed and potentially useful (soon to be licensed) second-line chemotherapy agents for ovarian cancer are needed. Such studies should also generate data for cost-effectiveness analysis – the economic results presented here suggest a potentially high value of additional information from further research. At present, it is difficult to make choices between pegylated liposomal doxorubicin hydrochloride and other drugs for second-line ovarian cancer treatment without such direct comparisons.

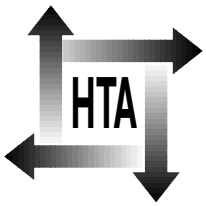
In view of the timescale required to conduct good quality RCTs and economic evaluations, and the fact that no such ongoing studies were identified, it seems reasonable not to update the current review until findings from such evaluations are available.

Reference

* Smith DH, Drummond MF, Johnston S, Gordon A. Economic evaluation of liposomal doxorubicin versus topotecan for recurrent ovarian cancer in the UK. *Value in Health* 2001;**4**:88.

Publication

Forbes C, Wilby J, Richardson G, Sculpher M, Mather L, Reimsma R. A systematic review and economic evaluation of pegylated liposomal doxorubicin hydrochloride for ovarian cancer. *Health Technol Assess* 2002;**6**(23).



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The research reported in this monograph was funded as project number 01/20/01.

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ISSN 1366-5278

Published by Core Research, Alton, on behalf of the NCCHTA.
Printed on acid-free paper in the UK by The Basingstoke Press, Basingstoke.