Evidence to support the clinical and cost effectiveness of Hycamtin®, GSK (topotecan) and Caelyx®, Schering-Plough (pegylated liposomal doxorubicin hydrochloride) for advanced ovarian cancer.

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Aims & Objectives

To assess the evidence relating to the clinical effectiveness and cost effectiveness of Hycamtin®, GSK (topotecan) and Caelyx®, Schering-Plough (pegylated liposomal doxorubicin hydrochloride) for the second-line treatment of ovarian cancer.

Introduction

Two drugs used in the treatment of ovarian cancer (Hycamtin® and Caelyx®) have recently been the focus of two separate appraisals by the National Institute for Clinical Excellence (NICE). As part of the appraisal process two separate systematic reviews of the evidence were commissioned. The following report summarises the findings of these reviews.

Background

Ovarian cancer is the most common of all the gynaecological cancers with an annual incidence of 21.6 cases per 100,000 women in England and Wales.(1) Due to the often asymptomatic nature of early disease, most cases of ovarian cancer are not detected until the advanced stages. Consequently, the prognosis after diagnosis is poorer than for other gynaecological cancers and figures suggest the five-year survival rate in the UK is only around 30%.(2-3) Current recommendations suggest that first-line chemotherapy for ovarian cancer patients should involve a platinum-based therapy (cisplatin/carboplatin) and paclitaxel.(4) However, the majority of patients develop resistant or refractory disease, which eventually requires second-line therapy. Patients may respond to re-challenge with platinum agents if the treatment-free interval is greater than 6 months, but often an alternative second-line therapy is required. Hycamtin and Caelyx are amongst six drugs currently licensed in the UK for second-line therapy.

Box 1. Inclusion criteria

a. Study design

- Randomised controlled trials (RCTs)
- Full economic evaluations

b. Interventions

Hycamtin/Caelyx used alone or in combination with other chemotherapeutic agents as second-line or subsequent therapy

c. Participants

Women with advanced ovarian cancer

d. Outcomes

- Progression free survival
- Overall survival
- Response (including complete and partial response)
- Symptom relief
- Quality of life
- Adverse effects
- Cost

Design

Two separate systematic reviews.

Methods

Although two separate systematic reviews were conducted, the reviews were carried out in a similar manner according to guidelines published by the NHS Centre for Reviews & Dissemination.(5) Both reviews are based on extensive literature searches, which also included submissions received from the drug manufacturers. Studies were selected according to the criteria shown in box 1. Full details of the two search strategies and the methods used in the reviews are available.(6-7)

Table 1. Summary of studies included in the reviews

a. Review of Hycamtin			
Study i.d.	**Study design**	**Comparators**	**Comments**
RCTs (n=2)			
039 (sponsored by GSK) (8-10)	Phase III, multi-centre RCT; 235 participants	Hycamtin vs. Paclitaxel	Main source of clinical effectiveness data for the review. Paclitaxel is no longer a relevant comparator as recommended for first-line therapy.
30-49 (sponsored by Schering-Plough)(11)	Phase III, multi-centre open-label RCT; 474 participants	Hycamtin vs. Caelyx	Main source of clinical effectiveness data for the review.
Economic evaluation(s) (n=3)			
039 (sponsored by GSK (unpublished)	Cost effectiveness analysis based on hypothetical group of 1000 patients.	Hycamtin vs. Paclitaxel	Main source of cost-effectiveness data for the review.
30-49 (sponsored by Schering-Plough)(12)	Cost minimisation analysis based on 474 participants in trial 30-49	Hycamtin vs. Caelyx	Main source of cost-effectiveness data for the review.
Bennett 1999 and Stinson 1999(13-14)	Cost-consequence analysis (participant numbers not stated).	Hycamtin vs. Paclitaxel vs. Etoposide vs. Altretamine	Not relevant to the UK NHS. Not used in assessment of cost-effectiveness.

b. Review of Caelyx			
Study i.d.	**Study design**	**Comparators**	**Comments**
RCTs (n=2)			
30-49 (sponsored by Schering-Plough)(11)	See topotecan review		Main source of clinical effectiveness data for the review.
30-57 (sponsored by Schering-Plough) (15)	Phase III, multi-centre open-label RCT.	Hycamtin vs. Paclitaxel	Trial was terminated. No outcome data available. Not used in assessment of clinical effectiveness.
Economic evaluation(s) (n=1)			
30-49 (sponsored by Schering-Plough)(12)	See topotecan review		Main source of cost-effectiveness data for the review.

* Six uncontrolled phase II studies were also included in the review but were not part of the main assessment of clinical effectiveness.

Results

Table 1 presents a summary of all the RCTs and economic evaluations satisfying the criteria for inclusion in the reviews.

Overall, both reviews rely on one international multicentre randomised controlled trial and accompanying economic evaluation (cost minimisation analysis) comparing Caelyx with Hycamtin (trial 30-49, 474 participants). Although of reasonable quality, these data were still subject to methodological flaws.

Overall, the evidence suggests there are no statistically significant differences between Hycamtin and paclitaxel or Hycamtin and Caelyx with regards to the main clinical outcomes (survival, response, quality of life) apart from the incidence of adverse effects (see Table 2). The effects of Hycamtin and Caelyx could at best be described as modest. However, Caelyx when compared to Hycamtin may offer the benefit of fewer side-effects and possibly improved cost-effectiveness.

Table 2. Summary of adverse events data comparing Hycamtin vs. Caelyx

Drug	Adverse event	Relative Risk (RR)
Favours Caelyx	Neutropenia	RR=2.313 (95% CI: 1.938, 2.793)
	Anaemia	RR=2.022 (95% CI: 1.683, 2.453)
	Thrombocytopenia	RR=4.987 (95% CI: 3.576, 7.048)
	Leukopenia	RR=1.742 (95% CI: 1.441, 2.122)
	Alopecia	RR=3.078 (95% CI: 2.251, 4.251)
	Nausea	RR=1.520 (95% CI: 1.238, 1.875)
	Vomiting	RR=1.420 (95% CI: 1.071, 1.891)
Favours Hycamtin	PPE	RR=0.017 (95% CI: 0.005, 0.063)
	Stomatitis	RR=0.375 (95% CI: 0.265, 0.525)
	Mucous membrane disorders	RR=0.216 (95% CI: 0.099, 0.466)
	Skin rashes	RR=0.316 (95% CI: 0.192, 0.514)

The economic evaluations suggest that Hycamtin may be more cost-effective than paclitaxel, but less so than Caelyx. Caelyx is less costly than Hycamtin (£9970, 95% CI: £9080, £10,861 vs. £12,627, 95% CI: 11,527, £13,727) and when effectiveness is based on survival duration Caelyx also has a high probability of being more cost-effective (70-80%) than Hycamtin. However, differences between the two therapies are likely to exist in overall health-related quality of life, which when expressed in terms of QALYs, could alter the cost-effectiveness findings markedly.

Conclusions

In conclusion, the limited evidence available suggests the effects of Caelyx and Hycamtin are at best modest. Evidence comparing the drugs with alternative treatments is very limited and suggests that such treatments offer little advantage. However, Caelyx may offer the possible benefit of fewer side effects and improved cost-effectiveness. Further good quality RCTs and economic evaluations comparing the drugs with each other and with other licensed or potentially useful (soon to be licensed) second-line chemotherapy agents are required. At present, it is difficult to make any informed decisions about the use of either drug for the second-line treatment of ovarian cancer without such good quality, direct comparisons.

NICE guidance

Subsequent to the completion of the two reviews, NICE has issued guidance recommending that Hycamtin and Caelyx be made available as options for the second-line (or subsequent) treatment of women with advanced ovarian cancer.

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