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Cost-Effectiveness of Trabectedin Plus Pegylated Liposomal Doxorubicin for the Treatment of Women with Relapsed Platinum-Sensitive Ovarian Cancer in the UK: Analysis Based on the Final Survival Data of the OVA-301 Trial

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ABSTRACT

Objectives: To estimate the cost-effectiveness of trabectedin plus pegylated liposomal doxorubicin (PLD) compared with PLD alone for the treatment of patients with relapsed platinum-sensitive ovarian cancer who are not expected to benefit from retreatment with platinum-based therapies based on the final survival data published in October 2012. **Methods:** A decision-analytic model estimated the cost per quality-adjusted life-year (QALY) gained for trabectedin plus PLD compared with PLD alone from the UK National Health Service and Personal Social Services perspective over a lifetime horizon. Mean progression-free survival and overall survival were calculated by using parametric survival distributions adjusted for imbalances discovered in the final survival data. Between-arm imbalances included the platinum-free interval, cancer antigen 125 (CA-125), and Eastern Cooperative Oncology Group performance score. Cost categories included drug, administration, medical management, and treatment of adverse events. Quality of life was measured by using the EuroQol five-dimensional questionnaire. Uncertainty was addressed by deterministic and probabilistic sensitivity analysis. **Results:** Over a lifetime horizon, trabectedin plus PLD increased mean progression-free survival by 3.0 months and overall survival by 9.7 months compared with PLD alone. The additional cost and QALYs of trabectedin plus PLD were £18,476 and 0.49, resulting in an incremental cost-effectiveness ratio of £38,026 per QALY. Sensitivity analyses showed that results were sensitive to platinum-free interval adjustment and the choice of survival distributions. **Conclusions:** The analysis estimated a significant improvement in mean overall survival and incremental cost per QALY compared with that calculated in the original National Institute for Health and Clinical Excellence assessment, which was based on immature survival data.

Keywords: cost-effectiveness analysis, decision analytic model, ovarian cancer, trabectedin, UK.

Introduction

The optimal treatment for women with relapsed ovarian cancer is evolving, and despite treatment advances, improvements in ovarian cancer survival rates have been modest, with a median survival after recurrence of just 2 years [1]. Patients with disease relapsing more than 6 months after completion of a platinum regimen are considered to have platinum-sensitive disease and are generally offered a platinum agent or platinum combination therapy [2]. Patients with longer relapse-free intervals are known to respond better to another exposure to platinum-based regimens. The relapse-free interval from which platinum exposure is not required is also known as the platinum-free interval (PFI), and is not to be confused with progression-free interval. One study that investigated retreatment with platinum compounds found PFI to be a significant predictor of response; 17% (6 of 35) of the patients who relapsed before 18 months responded as compared with 53% (10 of 19) who relapsed after 18 months ($P = 0.006$) [3]. There is, however, a significant number of patients with platinum-sensitive disease for whom retreatment with platinum-based agents is not recommended. These include patients developing toxicities, such as severe hypersensitivity reactions or neurotoxicity, as well as patients with a shorter PFI (<12 months) who are less likely to benefit from platinum retreatment [4,5]. Furthermore, it is becoming clear from various phase II and phase III clinical studies that the performance of many nonplatinum chemotherapeutic agents is also influenced by PFI [2] and for some patients with platinum-sensitive disease, the use of nonplatinum-containing regimens is an alternative treatment option. When nonplatinum treatment is planned, single-agent pegylated liposomal doxorubicin (PLD) (Caelyx; Janssen Biotech Inc., Horsham, PA) is usually used, and it has demonstrated superiority over topotecan and paclitaxel [6,7]. In the UK, current guidelines from the National Institute for Health and Clinical Excellence (NICE) recommend single-agent PLD as an option for women with partially platinum-sensitive disease and women with platinum-sensitive disease who are allergic to platinum-based compounds [8].

Trabectedin (Yondelis; PharmaMar, Madrid, Spain) is a marine-derived antineoplastic agent first approved as a single-agent

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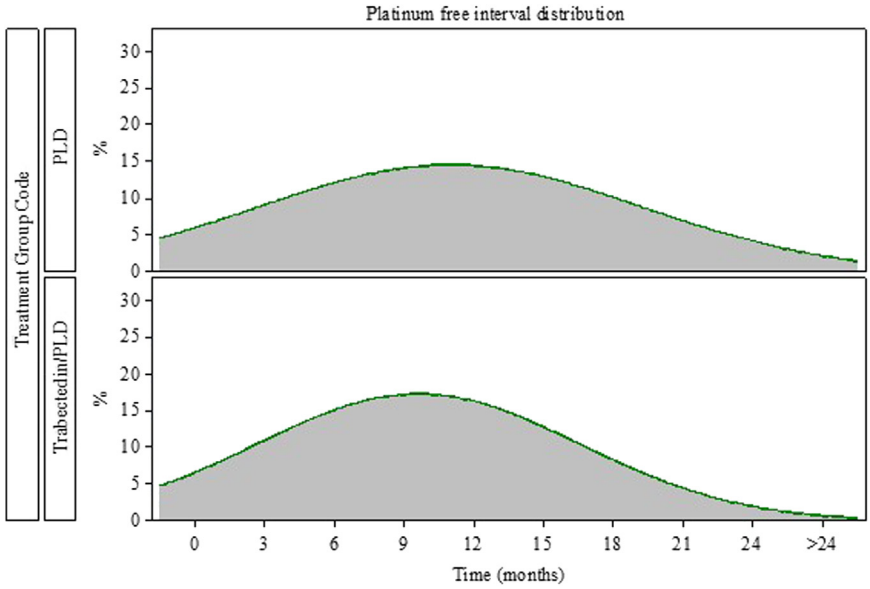

Fig. 1 – Distribution of platinum-free interval between the two arms. PLD, pegylated liposomal doxorubicin.

therapy for patients with soft-tissue sarcoma after failure of standard-of-care chemotherapies or who are unsuited to receive these agents. Following promising results in preclinical studies and as a single agent in phase II studies, a large randomized, multicenter, phase III trial (OVA-301) evaluated the combination of trabectedin plus PLD compared with PLD alone in patients with relapsed ovarian cancer (n = 672) and measured progression-free survival (PFS) by independent radiology review as the primary end point [9,10]. Patients included in the study had recurrent or progressive disease, experienced one platinum-containing regimen and were not expected to benefit, or were ineligible or not willing to receive retreatment with platinum-based therapy. Patients were stratified by Eastern Cooperative Oncology Group (ECOG) performance score (0–1 vs. 2) and platinum sensitivity of their disease (sensitive: PFI $\geq$ 6 months vs. resistant: PFI $<$ 6 months).

Trabectedin plus PLD significantly improved PFS compared with PLD alone, and was associated with a 21% risk reduction of progression (hazard ratio [HR] = 0.79; 95% confidence interval [CI] 0.65–0.96; $P = 0.019$; median PFS 7.3 vs. 5.8 months) and adequate tolerability. In the platinum-sensitive stratum, the risk reduction of disease progression was 27% (HR = 0.73; 95% CI 0.56–0.95; $P = 0.017$; median PFS 9.2 vs. 7.5 months). An interim analysis of overall survival (OS) was conducted with 419 events (vs. 520 required for the final analysis of OS [9]) on request from the European Medicines Agency and showed a 15% reduction in the risk of death with the combination (HR = 0.85; $P = 0.092$; median OS 22.4 vs. 19.5 months). Based on the PFS together with a positive trend in OS and a positive benefit/risk balance, the European Medicines Agency granted marketing authorization for trabectedin plus PLD for the treatment of patients with relapsed platinum-sensitive ovarian cancer in October 2009 [11].

A NICE submission was conducted for the platinum-sensitive population on the basis of the interim analysis during 2010 and it was concluded in April 2011 that there was not enough evidence to recommend trabectedin plus PLD [12]. This was primarily because the incremental cost-effectiveness ratio (ICER) for trabectedin plus PLD could be higher than £95,000 per quality-adjusted life-year (QALY) gained compared with PLD alone. It was, however, acknowledged that the submission was based on immature data because the prespecified number of events for final analysis of OS (520 events) had not been reached [9,12]. In addition, trabectedin plus PLD could not be compared with retreatment with platinum-based compounds, which is standard clinical practice in the platinum-sensitive population, and therefore comparing trabectedin plus PLD with PLD alone was considered clinically relevant only for circumstances in which platinum-based regimens would be unsuitable for platinum-sensitive patients [12].

In March 2011, 522 (77.7%) death events had occurred and the final protocol-specified analysis of OS was published in 2012 [10]. The final analysis reinforced the stronger trend for longer survival in patients treated with trabectedin plus PLD. Among the 430 platinum-sensitive patients, 316 (73.5%) death events were observed and there was a 17% reduction in the risk of death with the combination (HR = 0.83; 95% CI 0.67–1.04; $P = 0.106$; median OS 27.0 vs. 24.1 months). In addition, this analysis showed an unanticipated, yet significant, imbalance in the PFI favoring the PLD arm: in the entire trial population, the mean PFI for the trabectedin plus PLD arm was 10.6 months versus 13.3 months in the PLD arm, $P = 0.009$ (Fig. 1) [10]. When prognostic factors (including PFI) were included in the Cox regression model, the treatment with trabectedin plus PLD resulted in a 22% risk reduction of death compared with PLD alone, resulting in a 4.3 month improvement in median values (HR = 0.78; 95% CI 0.62–0.98; $P = 0.032$; median OS 28.4 vs. 24.1 months). The best-fitting survival model as measured by the C-statistic, adjusted for key prognostic factors including PFI, demonstrated a significant increase in OS for trabectedin plus PLD patients in the entire trial population (HR = 0.82; 95% CI 0.69–0.98; $P = 0.029$; median OS 22.2 vs. 18.9 months), which could potentially improve the cost-effectiveness of trabectedin plus PLD in the platinum-sensitive stratum [10].

The objective of this study was to investigate the cost-effectiveness of trabectedin plus PLD compared with PLD alone for patients with relapsed platinum-sensitive ovarian cancer who are not expected to benefit from retreatment with platinum-based therapies based on the final survival data from the OVA-301 trial.

Methods

A decision-analytic model was constructed in Microsoft Excel to estimate the costs and QALYs of a hypothetical cohort of patients with relapsed platinum-sensitive ovarian cancer from the UK