Paclitaxel: cost–effectiveness in ovarian cancer

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Ovarian cancer accounts for a significant burden of healthcare costs worldwide. Therapy of this disease consists of a combined surgical and chemotherapeutic approach. Remarkable advances in chemotherapy have been made with the introduction of new agents such as paclitaxel. Based on positive clinical data from randomized trials, numerous cost studies have been undertaken to analyze the cost–effectiveness of paclitaxel. Reviewing all the available cost studies, the authors conclude that paclitaxel plus cisplatin treatment is cost effective. Paclitaxel demonstrated survival and utility gains in combination with cisplatin as first-line treatment in patients with Stage II–IV ovarian cancer compared with cyclophosphamide and cisplatin. Incremental costs of US$6600–22,000 per life year gained are within an accepted range for new treatments.

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Malignant ovarian tumors derive from different types of cells of the ovary. They are grouped according to their origin of malignant transformation into three types: epithelial ovarian tumors, germ cell tumors and sex cord-stromal cell tumors. Epithelial ovarian tumors derive from malignant transformation of the epithelium of the ovarian surface. This type of tumor accounts for 90% of all malignant ovarian tumors [1]. In contemporary medical literature, the term ovarian cancer often encompasses solely the malignant epithelial ovarian tumors. Malignant germ cell tumors usually affect women of reproductive age and their management is completely different to treatment of epithelial ovarian cancer [2]. Epithelial ovarian cancers are classified according to their histologic types, the most common being papillary serous, endometroid, mucinous and clear cell carcinoma.

Epidemiology & diagnosis

Ovarian cancer is the fourth leading cause of cancer-related deaths in American women [3]. Approximately 22,220 new cases and 16,210 deaths related to ovarian cancer are estimated in the USA for 2005. Approximately nine to 12 new cases per 100,000 women are diagnosed in Western Europe yearly, and the annual death rate is between 3.6 and 9.3 per 100,000 women [4]. Long-term survival rates range from over 90% in early stages to 10–30% in advanced stages [5,6]. The median age of women diagnosed with ovarian cancer is approximately 60 years. Other known risk factors include family history, nulliparity, early menarche and late menopause [7]. Oral contraceptives, pregnancies and lactation are associated with reduced risk. Although positive family history is an important risk factor, a genetic predisposition is identified in only 5% of all cases. Currently, two gene mutations are known to cause high risk for development of ovarian cancer. The presence of an inherited mutation in *BRCA1* or *BRCA2* genes results in a lifetime risk of 16–44% for developing ovarian cancer and 56–87% for breast cancer, respectively [8,9]. A strong positive family history for breast and ovarian cancer should therefore suggest the presence of inherited *BRCA1/2* genes. Second, families with a predisposition for hereditary nonpolyposis colon cancer (HNPCC), endometrial and ovarian cancer could suggest the presence of a germline mutation of DNA mismatch repair genes, referred to as Lynch syndrome II [10].

The symptoms of ovarian cancer, including abdominal fullness, bloating and dyspepsia, are nonspecific and usually occur in the advanced stage disease because of increased abdominal

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pressure due to ascites [11]. Early stage disease is usually detected incidentally as an enlarged ovarian mass by transvaginal sonography in asymptomatic women [12]. Transvaginal sonography is currently the best tool for initial assessment of ovarian tumors. Complex ovarian cysts, which are defined by the presence of solid and cystic components, are highly suspicious for ovarian cancer. Another accurate radiologic modality for evaluation of ovarian masses is magnetic resonance imaging.

The role of various serologic markers in detection and screening of ovarian cancer have been extensively examined [13]. CA-125 is produced by most epithelial ovarian cancers and is currently widely used as a standard tumor marker for ovarian cancer. However, CA-125 like other tumor markers has the disadvantage of being an insufficiently sensitive and specific marker of ovarian cancer, which may be elevated in other nonmalignant gynecologic diseases such as endometriosis and pelvic inflammatory diseases. Furthermore, not all histologic types of ovarian cancer cause high CA-125 levels, for example mucinous and clear cell epithelial cancer. Thus, diagnosis of ovarian cancer should not be based on CA-125 levels. However, elevated levels in patients with suspicious ovarian cysts can raise the possibility of ovarian cancer. Additionally, the course of serum CA-125 levels is a very useful marker to assess the success of treatment and detect early relapse in patients with ovarian cancer and positive tumor marker. Screening with either sonography and/or CA-125 is currently unproven as a strategy for improving the detection and outcome for women with ovarian cancer. Ongoing prospective trials examining the role of screening a female population with transvaginal sonography and CA-125 are underway [14].

Table 1. Staging system for epithelial ovarian cancer.

Stage	Grade	Characteristics
I		Tumor limited to one or both ovaries
	A	One ovary involved, without ascites, positive peritoneal washings, surface involvement or rupture
	B	Both ovaries involved, without ascites, positive peritoneal washings, surface involvement or rupture
	C	Ascites, positive peritoneal washings, surface involvement or rupture present
II		Ovarian tumor with pelvic extension
	A	Involvement of the uterus or fallopian tubes
	B	Involvement of other pelvic organs (e.g., bladder, rectum or pelvic sidewall)
	C	Pelvic extension and findings indicated for Stage IC
III		Tumor involving the upper abdomen or lymph nodes
	A	Microscopic disease outside the pelvis, typically involving the omentum
	B	Gross deposits ≤2 cm in diameter
	C	Gross deposits >2 cm in diameter or nodal involvement
IV		Distant organ involvement, including pleura, liver and spleen

Surgery

Accurate staging of patients with suspected ovarian cancer can solely be performed by an exploratory laparotomy. In contrast to other gynecologic or nongynecologic cancers, no accurate preoperative staging modality exists. Through a vertical midline abdominal incision, both ovaries and as much of the tumor as possible, the uterus, the fallopian tubes, the omentum, the appendix, the pelvic and most often para-aortic lymph nodes are removed. Simultaneously, an optimal tumor debulking is performed (surgical cytoreduction) by removing as much macroscopic tumor as possible from the abdominal cavity. Furthermore, blind biopsies of the peritoneum and biopsies of suspected peritoneal lesions are performed. Finally, the whole abdominal cavity is washed with fluid (referred to as peritoneal washing/lavage), which is examined microscopically for cancer cells.

Histopathologic results of the removed specimen postoperatively determine the actual stage of disease (spread of the tumor beyond the ovaries) according to the classification system of the International Federation of Gynecology and Obstetrics (FIGO) (TABLE 1). The grade of the tumor cells (G1–3) is additionally determined using different criteria such as the architectural pattern of the cells or their nuclear content (DNA ploidy). Accurate staging and optimal tumor debulking is crucial as it determines the further treatment and survival of the patient and should be performed by experienced gynecologic oncologists. Retrospective studies have demonstrated that the amount of residual tumor after primary surgery is a prognostic factor. A recent meta-analysis revealed that maximal cytoreduction is one of the most powerful determinants of survival [15]. Patients with ovarian cancer not qualifying for explorative laparotomy and tumor debulking are those with coexisting severe diseases. This group of patients should receive a confirmatory biopsy and primary chemotherapy. If performance status improves, an interval cytoreduction can be considered.

First-line chemotherapy

Adjuvant chemotherapy is necessary in most patients with ovarian cancer in order to minimize residual disease after surgery. Only a small group of patients with Stage IA and Grade 1–2 disease do not benefit from adjuvant chemotherapy. Such patients with low-risk early disease have an excellent 5-year survival rate of 90–95% after surgery alone [6]. In all other stages, adjuvant chemotherapy with a taxane- and platinum-based chemotherapy is the current standard of care.

Cisplatin and cyclophosphamide was the standard treatment until the middle of the 1990s. In 1996, the Gynecologic Oncology Group (GOG) published results of the GOG 111

trial, which studied 386 women with Stage III suboptimal debulked or Stage IV disease [5]. Patients were randomized to receive either cisplatin 75 mg/m² plus paclitaxel 135 mg/m² over 24 h (CP) or cyclophosphamide 750 mg/m² every 3 weeks for a total of six courses (CC). The median follow-up was 37 months. Overall response rate was 73% in the CP group versus 60% in the CC group. Overall median survival was 38 months in the CP group – 14 months longer than in the CC group (TABLE 2).

However, treatment with paclitaxel was associated with increased toxicity. The incidence of neutropenia, febrile neutropenia, alopecia and peripheral neurotoxicity was significantly higher. These favorable results for the CP regimen were confirmed a number of years later by the Intergroup trial (TABLE 3) [16]. Selection criteria were wider including 775 women with FIGO Stage IIB, IIC, III or IV disease with or without successful debulking. The same drugs and dosages were administered in the Intergroup trial, with the exception that paclitaxel 175 mg/m² was infused over 3 h and for up to nine 3-weekly cycles. The median follow-up was 38.5 months. The overall response rate was 59 versus 45% in the CP and the CC groups, and overall median survival was 36 and 26 months, respectively. Both authors concluded that cisplatin plus paclitaxel is superior to the previous standard therapy using cisplatin plus cyclophosphamide [5,16]. Thus, taxane- and platinum-based regimens were introduced as first-line adjuvant therapy and remain the standard today.

Cisplatin is associated with significant neurotoxicity, ototoxicity and nephrotoxicity. As carboplatin, a similar compound, appeared to be better tolerated than cisplatin, comparative trials were initiated at the end of 1990 for carboplatin as an alternative taxane partner. The Dutch/Danish study in 208 patients and the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) study in 798 patients compared 3-weekly paclitaxel 175 or 185 mg/m² infused over 3 h plus cisplatin 75 mg/m² with the same dosage of paclitaxel plus carboplatin infused to achieve area under the curve (AUC) 5 or 6 [17,18]. Women in both studies had Stages IIB–IV disease and were followed up for a median of 37 months or a mean of 49–50 months. The GOG 158 trial in 792 patients with optimal Stage III disease compared paclitaxel 135 mg/m² infused over 24 h plus cisplatin 75 mg/m², with paclitaxel 175 mg/m² over 3 h plus carboplatin to AUC 7.5 [19]. All three studies showed similar response and survival rates, although nonhematologic toxicity was significantly lower in carboplatin-treated patients. Only granulocytopenia occurred more frequently in the carboplatin versus the the cisplatin arm. Therefore, carboplatin plus paclitaxel is considered as standard first-line therapy for ovarian cancer Stages II–IV.

Table 2. Clinical characteristics of Gynecologic Oncology Group 111 trial [5].

Parameters	Cisplatin and paclitaxel	Cisplatin and cyclophosphamide
Mean age in years (range)	59 (20–84)	60 (27–80)
Stage III patients	123	129
Stage IV patients	61	73
Regimen	Cisplatin 75 mg/m², paclitaxel 135 mg/m²	Cisplatin 75 mg/m², cyclophosphamide 750 mg/m²
Number of patients	184	202
Number of cycles	6	6
Response (%)	73	60
Median progression-free survival (months)	18	13
Median overall survival (months)	38	24

Second-line chemotherapy

Despite advances in new chemotherapy regimens described previously, most patients with advanced disease will develop recurrent disease. Such patients are incurable and their treatment should be considered as palliation. The goals of a second-line chemotherapy include improvement of symptoms, quality of life and prolonging of symptom-free survival. A major factor determining the possibility of a second-line chemotherapy is the patient's general health condition. Another crucial factor is the duration of the disease-free interval from first chemotherapy until relapse. Patients with tumor progression during first-line therapy or within 6 months of the treatment-free interval have the worst prognosis. Short relapse usually indicates platinum-resistant cancer. Thus, second-line treatment consists of a platinum-free single-agent regimen (e.g., topotecan, liposomal doxorubicin and gemcitabine). Advantages of these agents are improved tolerability and lower toxicity compared with a first-line regimen; however, response rate is poor, ranging from 10–20% [20]. Although no consensus for standard second-line therapy for platinum-resistant patients exists, liposomal doxorubicin is considered by many experts as the first choice due to its good efficacy and tolerability [21]. An alternative management for patients with advanced relapsed ovarian cancer is no further treatment, only palliation. Unfortunately, no comparative trials have been carried out determining the value of a second-line chemotherapy versus no treatment.

Patients with intermediate relapse have a disease-free interval of between 6 and 12 months after first-line therapy and are considered platinum sensitive. Treatment recommendations consist of using either initial regimen (carboplatin and paclitaxel) or a single-agent regimen. Patients presenting with a relapse more than 12 months after initial treatment have a favorable response to carboplatin and paclitaxel. Recently, the ICON4/AGO-OVAR-2.2 study demonstrated that a combination of paclitaxel with platinum led to significantly longer

Table 3. Clinical characteristics of the Intergroup trial [16].

Parameters	Cisplatin and paclitaxel	Cisplatin and cyclophosphamide
Regimen	Cisplatin 75 mg/m², paclitaxel 175 mg/m²	Cisplatin 75 mg/m², cyclophosphamide 750 mg/m²
Number of patients	342	338
Number of cycles	6	6
Response (%)	59	45
Median progression-free survival (months)	15.5	11.5
Median overall survival (months)	35.6	25.8

progression-free and overall survival compared with platinum alone in relapsed patients with platinum-sensitive disease [22]. Regarding quality of life after second-line chemotherapy, only few data are available so far, although it is a crucial point for the patient and for the cost–effectiveness of a given therapy [23].

Clinical profile of paclitaxel

Paclitaxel, the first taxane developed in clinical trials, is active against a broad range of cancers that are generally considered to be refractory to conventional chemotherapy. Paclitaxel has activity against a broad range of tumor types, including breast, ovarian, lung and head and neck cancers, and AIDS-associated Kaposi's sarcoma. Paclitaxel also has activity in other malignancies that are refractory to conventional chemotherapy, including previously treated lymphoma and small cell lung cancers and esophageal, gastric endometrial, bladder and germ cell tumors. The molecule was first isolated from the bark of the Pacific Yew tree (*Taxus brevifolia*). It disrupts the balance between tubulin and microtubule fibers, causing the formation of abnormal microtubule bundles. This prevents dividing cells from moving chromosomes to their daughter cells by interfering with spindle fiber formation [24].

Cost-effectiveness studies

An electronic search of the Medline database from 1966 to 2005 was performed to identify original research papers examining cost–effectiveness of paclitaxel for the treatment of ovarian cancer. Additionally, an electronic search of the abstract database of the *Proceedings to the Congress of the American Society of Clinical Oncology* (1995–2004) was performed. Studies published in nonpeer-reviewed journals were excluded. According to these search criteria, the authors identified nine original research papers that are included in this review [3,25–32]. Most of the cost–effectiveness studies of paclitaxel in ovarian cancer are based on clinical data of the GOG 111 and Intergroup trials. Although paclitaxel plus carboplatin is considered the standard treatment, no cost study with this regimen compared with CP or CC has been carried out to date. In the GOG 111 trial, a total of 386 patients had been included from the USA, while the Intergroup trial incorporated 680 patients from Europe and Canada. Cost–effectiveness studies have been conducted specifically for a number of countries for several healthcare systems.

USA

From the perspective of the US healthcare system, McGuire and colleagues accomplished a cost–effectiveness study using data from GOG 111 [28]. However, the resource use from this randomized controlled trial was corrected for real-world clinical practice according to a panel of clinical oncologists. Direct costs, such as hospitalization, drug acquisition, physician visits, adverse events and their follow-up, in- and out-patient treatment facilities, diagnostic and laboratory tests were included. In contrast to the GOG111 data, where chemotherapy was administered in an in-patient setting, costs were also calculated for out-patient treatment. The drug costs did not differ between in- and out-patient groups. Drug cost for six cycles amounted to US$10,615 for CP regimens, whereas costs of the CC regimen totaled US$3221. Savings were in the region of US$2504 for out-patient treatment in the CP collective. In the CC group, an out-patient treatment reduced costs to US$3182.

Total costs for CP resulted in US$29,824 for in-patient and US$27,320 for out-patient treatment. For the CC group, in-patient costs were US$21,086 and out-patient costs were US$17,964.

Estimating mean time survival according to GOG 111 at 2.76 for the CP and 2.32 for the CC groups, the incremental costs per life-year gained (LYG) was US$19,820 for in-patient and US$21,222 for out-patient treatment with CP instead of CC treatment. McGuire and colleagues concluded that the incremental cost–effectiveness values were well within the accepted ranges for a new treatment.

A second study conducted by Messori and colleagues evaluated the lifetime costs of paclitaxel from the perspective of the US society [29]. Only direct costs were included and only incremental costs of the paclitaxel treatment (treatment for febrile neutropenia, hospitalization and drug administration) were estimated, rather than absolute costs. Unit costs for hospitalization, treatment of febrile neutropenia and out-patient visits were transferred from published literature. Survival data obtained from GOG 111 was extrapolated based on the Gompertz equation. Thus, an improved life expectancy of 0.46 years was incorporated into the analysis for the CP group. The incremental costs per patient for the CP treatment totaled US$13,020 and US$4003 for CC. The incremental cost–effectiveness ratio (ICER) generated for CP was US$19,603 per LYG. The ICER per discounted LYG amounted to US$20,494.

Canada

Four further studies from Canada attempted to determine the cost–effectiveness of paclitaxel from the perspective of the Ministry of Health in Ontario, where there is a fixed budget for cancer.

Elit and colleagues created a decision tree model to compare the cost–effectiveness [26]. In defined health states (death during 6 months of chemotherapy; death after chemotherapy completed, but before 5 years; and survival beyond 5 years), the patients could develop major, minor or no adverse events. The probabilities were prepared for the known CP and CC regimens and costs were computed for each of the prescribed decision trees. Direct costs, such as hospitalization, drug acquisition and major adverse events, such as allergies and physician services, were based on 1993 local unit costs in Ontario. Use of resources was assessed by the experience of clinicians, rather than retrospective chart review in contrast to other studies. The effectiveness outcome parameter was mean survival, extrapolated to 48 months from data of the GOG 111 trial.

The assumed mean survival for the CP group was 2.44 years and 2.06 years for treatment with CC. The total cost per patient amounted to CAN$17,469 for CP and CAN$5228 for CC. The ICER for the combination of CP and CC resulted in CAN$32,213 per LYG. Since Ontario fixed the budget for cancer care, the incremental costs for the introduction of CP as first-line treatment would not be possible without offsetting other areas of oncology treatment. This first-line treatment would require an additional CAN$9 million per year for Ontario.

Covens and colleagues analyzed retrospective data from 18 patients treated with CC for suboptimal Stage IIIC/IV epithelial ovarian cancer in Ontario [33]. CC had been administered in 50 and 500 mg/m^2 (GOG 111 used 75 and 750 mg/m^2). The mean survival rate for CP was 1.98 months compared with 1.31 years for CC, assuming a 50% increase of survival based on GOG 111 results. The included direct costs were obtained from one cancer center in 1993 prices. Thus, the costs of patients visiting other physicians outside the center were not recorded.

The total costs per patient for CP rose to CAN$50,054, whereas for CC, the costs amounted to CAN$36,837. The ICER for paclitaxel (infusion over 3 h) resulted in CAN$20,355 per LYG. The investigators found this favorable compared with other interventions, for example, chemotherapy, renal transplantation or dialysis.

For the Canadian national health service provider, Walker and colleagues employed the resource use of 160 Canadian patients participating in the Intergroup trial and calculated costs based on the data from a major medical center [32]. Total lifetime costs per patients from randomization to death were assessed, excluding second-line treatment costs. Effectiveness data were based on the median-progression free and overall survivals of the Canadian group of patients. Walker and colleagues found a median progression-free survival of 1.42 years, an overall survival of 3.07 years for CP and total costs of US$30,774 per patient. Therapy with CC arose to a median progression-free survival of 0.84 years and overall survival of 2.13 years. The charges for this combination amounted to US$18,515. The ICER per LYG for a mean survival was US$13,135 and US$21,312 for mean progression-free survival.

Ortega and colleagues conducted a cost–utility analysis from the perspective of the Canadian healthcare system [31]. Survival data from the GOG 111 trial were supplemented with quality of life data. The group matched 12 patients for age and disease stage (I–II) receiving CP treatment with CC patients. Total hospital costs were totaled and treatment preferences had been evaluated from a 20-patient cohort as well as from 40 healthy voluntary females by using the time trade-off method. Outcomes were constructed using a decision model. This model for patients presenting Stage III/IV began with the choice of first-line chemotherapy of either CP or CC. After six treatment cycles, CC nonresponders received single-agent paclitaxel. CP patients who failed to respond were offered a second-line therapy with ifosfamide, tamoxifen or altretamine. For cost calculation, a retrospective chart review of 12 CP patients was matched with CC control patients. In a third cohort, 49 patients had been chosen to be treated with second-line therapy. CP treatment costs (CAN$1.911) were fourfold greater than expenses in the CC group (CAN$459). The incremental cost–utility ratio for CP of CAN$11,600–24,200 per quality-adjusted life-years gained (QALY) depended on the choice of second-line treatment.

Europe

In Europe, Berger and colleagues performed a cost–effectiveness analysis conducted from the view of the national health service payers of France, Germany, Italy, The Netherlands, Spain and the UK [25]. Country-specific data on treatment patterns and costs were constructed for each country. The basis of the data were furnished by interviews with expert panels in each country. Drug prices were taken from hospital pharmacists and official price lists. Costs included in this investigation were charges of hospitalization, consultations, adverse events, laboratory tests and drug acquisition. As basis of the survival data, the authors used the declining exponential approximation of life expectancy (DEALE) method. This involves calculating the specific patient life expectancy from the disease-specific mortality rate and the mortality rate of the standard population of a given gender and age, regarding the country-specific data. The GOG 111 trial provided ages and disease-specific mortality. For patients who received a treatment with paclitaxel and cisplatin, the survival rate in years resulted as follows: France 3.88 years, Germany 3.83 years, Italy 3.85 years, The Netherlands 3.85 years, Spain 3.86 years and the UK 3.82 years.

The CC-treated patients demonstrated a life expectancy of 2.58 years in France. Results appeared to be similar for the other countries: Germany 2.56 years, Italy 2.57 years, The Netherlands 2.57 years, Spain 2.57 years and the UK 2.55 years. Compared with this small-scale spread, the results for the total costs diversified to a greater extent.

The baseline and sensitivity analysis compared the incremental costs and benefits of CP over CC when used as a first-line treatment for advanced ovarian cancer. This created a best-case, baseline and worst-case scenario. A best case implies a decrease in survival of 50% with the combination of paclitaxel and cisplatin while the costs of paclitaxel decreased by

approximately 20%. A worst-case scenario showed a decrease in survival of 50% in the CP group and a boost of paclitaxel costs of 20%.

The authors demonstrated an ICER within acceptable limits. In this investigation, the highest value of US$26,558 per LYG was calculated in the Italian system, when the incremental survival was decreased by 50% and the drug costs of paclitaxel and cisplatin increased by 20% (TABLE 4).

Neymark and colleagues attempted to estimate cost–effectiveness of paclitaxel for the Belgian health insurance system [30]. Resource use was collected from 231 patients recruited from the European Organization for Research and Treatment of Cancer (EORTC) out of the 680 patients of the Intergroup trial. Resource use included hospitalization, chemotherapy cost and second-line treatment. In addition, more detailed cost data were obtained from 64 patients participating in a special economic case report form collecting number of out-patient consultations, diagnostic test and concomitant medication. These data were considered representative for the entire 231 patients recruited by EORTC. Unit costs expressed in 1998 prices were obtained from Belgian healthcare providers. Mean survival was calculated at 30.6 months for the CP group and 26.6 months for the CC group. Total costs for the combination of CP were estimated at €23,324 and €16,529 for CC. Thus, ICER resulted at €20,385 per LYG, assuming a mean survival benefit of 4 months. If all newly diagnosed Belgian patients were treated by the CP regimen, total incremental costs for the Belgian healthcare system would rise to approximately €4.1 million per year. Despite inclusion of costs for second-line chemotherapy, the ICER per LYG was similar to the results of other trials.

Limat and colleagues compared the cost–effectiveness of CP versus CC for French healthcare providers [27]. In contrast to the other cost–effectiveness studies, survival data were obtained retrospectively by patients' chart review and not from randomized controlled trials such as the GOG 111 or Intergroup OV10. Furthermore, results were expressed in cost–effectiveness ratio as well as in cost–utility ratios. This group carried out a before/after case study in order to measure clinical outcomes and costs. A total of 59 women with FIGO Stage IIC, III or IV treated in a French university hospital (Besançon) were retrospectively included. The investigators calculated costs for each patient from the perspective of the hospital payer perspective. Median overall survival was the primary end point. The examiners quantified the quality-adjusted time by the quality-adjusted time without symptoms or toxicity (Q-TwiST) method. This time was defined from the end of the first-line chemotherapy to the first observation of progressive disease.

Monetary values for French prices in the year 2000 were used and converted to US$ by using an exchange rate of US$ equals FR 7. The unit prices (2000 values) amounted to US$0.85 for cyclophosphamide, US$7.85 for cisplatin and US$457 for paclitaxel. In the CC group, there were more patients presenting FIGO Stage III and IIIA (3 vs. 0 in CP), while the CP group had more patients with FIGO Stage IIIC (22 vs. 19 in CC). The average length of hospital stay was longer for the paclitaxel than for the cyclophosphamide collective (22.1 vs. 14.3 days). Consequently, the mean charges for hospitalization were higher for the paclitaxel patients (US$7349 vs. US$4796). The mean amount for the chemotherapy was US$6566 for the paclitaxel group and US$692 for the patients treated with cyclophosphamide. The resulting mean overall costs (including anti-infectious agents, blood products and hematopoietic growth factors) amounted to US$17,514 for the CP combination and US$6798 for the combination of CC.

The progression-free survival was 11.2 months (CC) versus 14.2 months (CP), while the median overall survival was 21.2–32 months. The clinical benefit of a first-line therapy with CP had been 0.9 years in this group. The ICER of CP was found to be US$11,907 per LYG and US$13,827 per QALY. This amount should be within acceptable ranges for French university hospitals according to Limat and colleagues.

Expert commentary

Most of the composed pharmacoeconomic examinations the authors reviewed had a focal point on first-line therapy of advanced ovarian cancer. As the authors focused their review on Medline search, further evidence (i.e. nonpeer-reviewed, non-Medline indexed) may have been omitted. All of the cost studies demonstrated a survival advantage for cispaltin and paclitaxel. In the USA and Canada, ICERs resulted from US$13,135–25,131 per LYG. In European countries, lower ICERs had been reported except for in Belgium (US$9103–23,234 per additional LYG). The range extended from US$6395 for Spain up to US$11,420 for Italy (TABLE 5).

However, all cost–effectiveness studies are based on the CP regimen, despite not being the standard of care. Unfortunately, no cost study on the current first-line standard treatment, carboplatin

Table 4. Incremental costs for paclitaxel treatment in Europe (US$) [25].

Category of costs	France	Germany	Italy	The Netherlands	Spain	UK
Total costs for CP	17,150	24,487	21,230	16,547	17,520	13,038
Total costs for CC	8502	12,578	6578	6537	9290	4926
Incremental costs	8648	11,909	14,652	10,010	8230	8112
Costs per life-year saved	6642	9362	11,420	7796	6395	6403

CC: Cisplatin plus cyclophosphamide; CP: Cisplatin plus paclitaxel.

Table 5. Summary of cost–effectiveness studies comparing paclitaxel plus cisplatin with cyclophosphamide plus cisplatin for first-line treatment of advanced epithelial ovarian cancer.

Cost perspective	Incremental cost per LYG	Incremental cost per QALY gained	Survival benefit for CP group	Ref.
Studies based on GOG 111 trial				
National healthcare provider				[25]
France	US$6642		1.30	[25]
Germany	US$9362		1.27	[25]
Italy	US$11,420		1.28	[25]
The Netherlands	US$7769		1.28	[25]
Spain	US$6395		1.28	[25]
UK	US$6403		1.27	[25]
US Healthcare provider			0.44	[28]
In patient	US$19,820			[28]
Out patient	US$21,222			[28]
Societal perspective lifetime costs	US$19,603		0.46	[29]
Provincial perspective (ON, Canada)	CAN$32,213		0.38	[26]
Provincial perspective (ON, Canada)	CAN$20,255		0.67	[33]
Studies based on the Intergroup trial				
Belgian healthcare provider		€20,385	0.33*	[30]
Canadian healthcare provider		US$13,135	0.94	[32]
Hospital database				
French university hospital	US$11,907	US$13,827	0.90	[27]
Canadian healthcare provider			0.84†	[31]
Ifosfamide		CAN$24,200		[31]
Tamoxifen		CAN$11,600		[31]
Altretamine		CAN$14,800		[31]

*Restricted means method.
†Quality-adjusted progression-free years.
CP: Cisplatin plus paclitaxel; GOG: Gynecologic Oncology Group; LYG: Life-year gained; QALY: Quality-adjusted life years.

plus paclitaxel, is available. This combination is believed to have a more favorable side-effect profile than CP [17,18]. Although drug acquisition costs of cisplatin and carboplatin do not differ significantly, differences in cost–effectiveness should be determined given the unequal side effects.

In spite of different approaches, relatively similar results have been obtained. This confirms the robustness of the reported ICER findings. Paclitaxel has demonstrated survival and utility gains in combination with cisplatin compared with cyclophosphamide and cisplatin as first-line treatment in patients with Stage III or IV ovarian cancer. Incremental costs (US$6600–22,000) are within the accepted range compared with incremental costs for other oncologic and life-saving therapies. The presumed upper range for the ICER of US$50,000 is equivalent to the acceptable consensus. However, cost–effectiveness and quality of life in cancer treatment will become more important in the future due to high expenses of societal healthcare stress.

To date, comprehensive work on cost–effectiveness and cost–utility of paclitaxel for ovarian cancer has been conducted. Data on many specific healthcare systems is available. Nevertheless, further research is warranted. More cost–utility studies with assessment of quality of life and costs should be established, although cost–effectiveness and cost–utility in interventions for cancers often correlates [34].

Maximization of survival outcomes does not always result in an upgrade of quality of life. Side effects are crucial for determining the quality of life of patients. More research in this

direction is needed in the future, given the lack of available quality-of-life data, especially for second-line chemotherapy in ovarian cancer. Furthermore, costs for treatment of side effects can shift a treatment with a low-priced drug towards a cost-ineffective treatment. As paclitaxel demonstrated a delay in disease progression, prolongation of good quality of life and longer survival cost studies resulted in a favorable economic profile for this drug.

Many of the available workings had been carried out from the perspective of health service providers. The few studies carried out from a societal perspective did not take the important indirect socioeconomic costs into consideration. It is known that even indirect costs account for 68% of the total expenses for ovarian carcinoma [35]. Further cost–effectiveness studies should also address the issue of indirect costs. Differences in productivity loss, for example, can significantly influence cost–effectiveness ratios of treatments.

No data is currently available regarding cost–effectiveness studies on paclitaxel for second-line treatment, considering that paclitaxel is only used for second-line treatment if recurrence occurs after 6–12 months (platinum-sensitive recurrence) and that alternative second-line chemotherapy regimens are available.

Five-year view

Many new oncologic therapies are currently under experimental and clinical investigation [36]. For ovarian cancer, the authors believe that over the next 5 years the platinum/taxane combination will remain the standard of care. A newer taxane being examined versus paclitaxel in ovarian cancer patients, namely docetaxel, failed to show a significant improvement in either efficacy or tolerability [37]. Thus, the authors do not expect paclitaxel to be substituted by other taxanes in the near future. The introduction of a third partner to paclitaxel and carboplatin is more likely, assuming that the triple combination has acceptable toxicity and proven benefits. Various randomized controlled trials examining a third compound in addition to CP are underway [38,39].

Expiry of patent rights on paclitaxel and the emergence of generic versions in different countries may lead to lower drug acquisition costs [40]. Thus, cost–effectiveness would result, of course, in a much more favorable range. Furthermore, different formulations of paclitaxel (e.g., oral formulation) could improve clinical efficacy and thus cost–effectiveness or shift in patient administration of chemotherapy towards out-patient treatment, resulting in lower hospitalization costs [41,42].

Key issues

- Many comprehensive cost–effectiveness studies have been carried out to date for paclitaxel plus cisplatin based on clinical data from randomized controlled trials.
- No cost–effectiveness data on the current first-line combination of paclitaxel plus carboplatin is available.
- All studies consistently show acceptable incremental cost–effectiveness ratios across different healthcare systems.
- Unfortunately, no data are available on the impact of paclitaxel on indirect costs.
- No data are yet available on the cost–effectiveness of paclitaxel in second-line treatment.

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