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Economic evaluation of new drugs

Pharmacoeconomic profile of taxanes in advanced ovarian cancer

Andrea Messori and Sabrina Trippoli
Drug Information Centre, Pharmaceutical Service, Careggi Hospital, Azienda Ospedaliera Careggi, viale Morgagni 85, 50134 Florence, Italy. Tel: (+39) 055 4279230; Fax: (+39) 055 4279738.

This article reviews the information currently available on the pharmacoeconomic profile of taxanes in ovarian cancer. Because paclitaxel is the only taxene approved for this clinical indication, our overview is almost entirely focused on the cost–effectiveness profile of this drug. In advanced ovarian cancer, first-line regimens based on paclitaxel have been reported to be more effective than standard therapy based on cyclophosphamide + cisplatin. The improved survival with paclitaxel and the increased cost induced by this drug have prompted a series of pharmacoeconomic analyses, the results of which are summarized and discussed. Three studies, published between 1996 and 1997, calculated the cost per life-year gained using paclitaxel + cisplatin as opposed to cyclophosphamide + cisplatin. The estimates of survival gain and increased expenditure using paclitaxel were very similar; consequently, the results produced by these three analyses were homogeneous with values of cost per life-year gained around $20 000. Because this value is below the conventional limit of $50 000, the pharmacoeconomic results on paclitaxel suggest a favorable cost–effectiveness profile. Docetaxel is another taxane proposed for the treatment of advanced ovarian cancer; however, the drug has not yet been approved for this clinical indication and so a pharmacoeconomic assessment on this agent is still premature. [© 1998 Lippincott Williams & Wilkins.]

Key words: Advanced ovarian cancer, docetaxel, paclitaxel, taxane.

Introduction

A high proportion of cases of ovarian carcinoma are diagnosed when the disease is already in an advanced phase (stage III or IV). For this reason, many clinical trials in patients with ovarian carcinoma have been conducted to test innovative approaches specifically aimed at treating advanced disease.

Until recently, cisplatin has been the mainstay of chemotherapeutic protocols for advanced ovarian carcinoma. A high percentage of response was generally observed using cisplatin-based first-line regimens (about 70%), but the subsequent relapse rates were disappointing. In the late 1980s and in the early 1990s, the combination of cyclophosphamide + cisplatin became the standard first-line treatment even though this regimen ensured a long-term disease-free rate of less than 10% in stage III and less than 5% in stage IV.[1]

In 1989, McGuire *et al.*[2] undertook a phase II clinical trial to evaluate paclitaxel in patients showing no response to cisplatin. These preliminary results were then confirmed by further phase II studies coordinated by the Gynecologic Oncology Group (GOG). Overall, this phase II experience with paclitaxel in advanced ovarian carcinoma was encouraging[2,3] and prompted the GOG to start a prospective randomized phase III trial (GOG111) to compare paclitaxel + cisplatin with the standard regimen of cyclophosphamide + cisplatin.[4] A total of 386 women with advanced ovarian cancer were enrolled in this trial and were randomly assigned to one of the two following treatments: the first group (n=202) was treated with cyclophosphamide (750 mg/m^2 i.v. over 2 h) and cisplatin (75 mg/m^2 i.v.) while the second group (n=184) was treated with paclitaxel (135 mg/m^2 i.v. over 24 h) and cisplatin (75 mg/m^2 i.v.). Both of these treatments were administered every 3 weeks. A total of six cycles per patient were planned by the trial's protocol.[4]

The result of the GOG111 trial showed that the patients treated with paclitaxel + cisplatin had a significantly better survival than those assigned to the reference chemotherapy (median survival=18 months in the paclitaxel + cisplatin group versus 13 months in the cyclophosphamide + cisplatin group).[4] This finding of an improved survival with paclitaxel and the evidence of an increased cost by adopting this innovative chemotherapy prompted several researchers to undertake a series of pharmacoeconomic

Correspondence to A Messori

analyses. Because three studies have been published over the past 2 years on this subject,[5-7] this article attempts to summarize the information reported in these three pharmacoeconomic contributions. The information available on the pharmacoeconomic profile of other forms of taxane therapy in ovarian cancer (e.g. docetaxel and i.p. paclitaxel) is still incomplete or even completely lacking. Hence, our article is almost completely focused on the paclitaxel + cisplatin regimen tested in the GOG111 trial.

Overview of three pharmacoeconomic studies on first-line paclitaxel in advanced ovarian cancer

Design and results of the three pharmacoeconomic studies

The three pharmacoeconomic studies examined herein[5-7] were all based on the clinical results produced by the GOG111 trial.[4] The three pharmacoeconomic analyses were very similar in their respective methodology. All three studies were in fact aimed at determining the incremental cost (defined as the mean post-randomization cost per patient in the paclitaxel + cisplatin group minus the mean post-randomization cost per patient in the cyclophosphamide + cisplatin group) and the incremental effectiveness (defined as the mean post-randomization survival per patient in the paclitaxel + cisplatin group minus the mean post-randomization survival per patient in the cyclophosphamide + cisplatin group) in order to calculate the consequent cost-effectiveness ratio (CER) according to the following equation:

$$\text{CER} = \text{incremental cost}/\text{incremental effectiveness} \quad (1)$$

where CER is expressed as cost per life-year gained using paclitaxel + cisplatin as opposed to cyclophosphamide + cisplatin.

In the work of Elit *et al.*,[5] the analysis of cost data considered three separate patient groups: (i) patients who lived less than 6 months, (ii) patients who lived more than 6 months but less than 5 years and (iii) patients who lived more than 5 years. In this framework, the average cost per patient was determined on the basis of this stratification of the patients across these three outcome categories. The items considered by Elit *et al.*[5] in their estimation of costs referred to the state of Ontario in Canada, and included costs related to the administration of chemotherapy, drug acquisition costs, hospitalization costs, diagnostic procedures, costs induced by drug-related side effects and follow-up costs (expressed in terms of cost of periodic visits). Cost data of Elit's work were all subjected to an annual discount rate of 5%. The economic analysis of Elit *et al.* (Tables 1 and 2) showed that the average post-randomization cost per patient was $17 469 for paclitaxel + cisplatin versus $5228 for cyclophosphamide + cisplatin (Canadian $).

In their survival assessment, Elit *et al.*[5] utilized a simplified method that employed a mathematical integration of the areas under the survival curve (AUCs) reported by McGuire *et al.*[4] for the two treatments. This mathematical integration considered only the time interval from randomization to the last time-point in the follow-up (at 48 months) and so it employed no extrapolation to account for residual survival after 48 months. The incremental effectiveness (or survival gain using paclitaxel + cisplatin as opposed to cyclophosphamide + cisplatin) was then estimated as the difference between the two values of AUC. Mean survival was 2.44 years per patient for paclitaxel + cisplatin versus 2.06 years per patient for cyclophosphamide + cisplatin (Table 3) with a survival gain of 0.38 years per patient (data with 5% annual discounting). On the basis of these data of incremental cost and incremental effectiveness, the CER calculated by Elit *et al.*[5] acccording to equation (1) (Tables 3 and 4) was $32 213 per life-year gained (Canadian $).

In the economic study by McGuire *et al.*,[6] the cost items introduced in the analysis included: (i) the cost of anti-neoplastic agents (acquisition costs and administration costs), (ii) the cost of anti-hypersensitivity drugs, (iii) the cost for treating chemotherapy-related side-effects (febrile neutropenia, alopecia and hypersensitivity reactions), and (iv) the cost of periodic visits, diagnostic procedures, equipment and follow-up. McGuire *et al.*[6] utilized primary cost data obtained from the patient series enrolled in the GOG111 study;[4] in their pharmacoeconomic study the same patient cohort therefore was the source of both clinical and economic data.

The results produced by the analysis of McGuire *et al.*[6] were the following (Table 1). The group treated with paclitaxel + cisplatin had a cost of $29 824 per patient in cases requiring hospitalization or $27 320 per patient in cases not requiring hospitalization, whereas the group treated with cyclophosphamide + cisplatin had a cost of $21 086 per patient (with hospitalization) or $17 964 per patient (without hospitalization). All these values include 4% annual discounting.

The survival gain between the two treatment groups was estimated as the difference between the two values of AUC.[6] Also in this study, no extrapolation of

Table 1. Cost per patient of first-line chemotherapy with paclitaxel + cisplatin estimated in three different pharmacoeconomic analyses (see text for details)

	Drug acquisition cost, cost of chemotherapy administration and hospitalization cost ($ per patient)	Cost for treating chemotherapy-related side effects ($ per patient)	Follow-up cost ($ per patient)	Total cost ($ per patient)
Elit *et al.*[5]	16839[a]	398[a]	229[a]	17469[a]
McGuire *et al.*[6]				
in-patients	24307	640	4877	29824
out-patients	21803	640	4877	27320
Messori *et al.*[7]	11820	1200	–	13020

[a]Values for this study are expressed in Canadian $.

Table 2. Cost per patient of first-line chemotherapy with cyclophosphamide + cisplatin estimated in three different pharmacoeconomic analyses (see text for details)

	Drug acquisition cost, cost of chemotherapy administration and hospitalization cost ($ per patient)	Cost for treating chemotherapy-related side effects ($ per patient)	Follow-up cost ($ per patient)	Total cost ($ per patient)
Elit *et al.*[5]	4843	200	185	5228
McGuire *et al.*[6]				
in-patient	16913	257	3917	21086
out-patient	13791	257	3917	17964
Messori *et al.*[7]	3363	640	–	4003

[a]Values for this study are expressed in Canadian $.

Table 3. Survival data of the GOG111 study introduced in the three pharmacoeconomic analyses

	Mean survival (years per patient)				Survival gain (years per patient)	
	Paclitaxel + cisplatin group		Cyclophosphamide + cisplatin group		Discounted	Undiscounted
	Discounted	Undiscounted	Discounted	Undiscounted		
Elit *et al.*[5]	2.44	–	2.06	–	0.38	–
McGuire *et al.*[6]	–	2.76	–	2.32	–	0.44
Messori *et al.*[7]	2.74	2.95	2.31	2.50	0.43	0.45

the two curves after the last time-point of the follow-up was carried out. The values of mean post-randomization survival were 2.32 years per patient for the cyclophosphamide + cisplatin group versus 2.76 years per patient for the paclitaxel + cisplatin group. The survival gain was 0.44 years per patient (Table 3).[6]

These data of cost and survival give rise to a cost-effectiveness ratio of $19 860 per life-year gained for hospitalized patients ($29 824 − $21 086 divided by 0.44 years[6]) and of $21 264 per life-year gained for non-hospitalized patients ($27 320 − $17 964 divided by 0.44 years[6]), both calculated according to equation (1) (Table 4).

In the work of Messori *et al.*,[7] the cost for the two treatment modalities included: (i) drug acquisition cost for antineoplastic agents, (ii) costs for acquisition and administration of anti-hypersensitivity drugs (diphenhydramine, ranitidine and dexamethasone), (iii) hospitalization costs (calculated on the assumption of a 24 h duration of paclitaxel infusion) and (iv) cost for treating chemotherapy-induced side effects (i.e. febrile neutropenia). All data assumed 5% annual discounting.

The total cost per patient was estimated as $13 020 for paclitaxel + cisplatin (Table 1) and $4003 per patient for cyclophosphamide + cisplatin (Table 2) with an incremental cost of $9017 per patient.[7]

Table 4. Values of incremental cost and cost per life-year gained

	Incremental cost (discounted $ per patient)	Cost per life-year gained	
		Discounted $ per discounted years	Discounted $ per undiscounted years
Elit *et al.*[5]	12241[a,b]	32312[a,b]	–
McGuire *et al.*[6]			
in-patient	8738[c]	–	19860[c]
out-patient	9356[c]	–	21264[c]
Messori *et al.*[7]	9017[b]	20969[b]	20037[b]

[a]Values for this study are expressed in Canadian $.
[b]With 5% annual discounting.
[c]With 4% annual discounting.

The survival analysis of Messori *et al.*[7] utilized a traditional AUC analysis combined with an extrapolation of the survival curves to infinity based on Gompertz' equation.[8] The values of mean post-randomization lifetime survival (or AUC) were 2.95 undiscounted years (or 2.74 discounted years with a discount rate of 5% per annum) for the paclitaxel + cisplatin group and 2.50 undiscounted years (or 2.31 discounted years) in the cyclophosphamide + cisplatin group (Table 3). The survival gain was estimated from the difference of the two AUC values.[7]

Using equation (1), the CER (Table 4) was estimated as $20 037 per life-year gained (undiscounted) or $20 969 per life-year gained (with 5% annual discounting).[7]

Survival gain using first-line paclitaxel

In the three studies of Elit *et al.*,[5] McGuire *et al.*[6] and Messori *et al.*,[7] the estimates of the survival gain obtained with the paclitaxel regimen were very similar (Table 3). This similarity in the survival analysis could be expected because the clinical material introduced in these three studies was exactly the same, i.e. the patient cohort enrolled in the GOG111 study. In addition, the techniques for handling the survival data were similar because all three studies were based on AUC estimations. The extrapolation of the survival curves after the last time-point of the follow-up (i.e. the extrapolation from 48 months to infinity) was employed in the analysis of Messori *et al.*[7] (who utilized the Gompertz extrapolation technique[8]), but not in the analyses of Elit *et al.*[5] and of McGuire *et al.*[6] This difference, however, had a negligible impact on the estimation of the survival gains, probably because the life expectancy of patients with advanced ovarian cancer is short and the inclusion or not of the contribution of residual survival after 4 years had a small influence on the survival gain values.

Incremental cost using first-line paclitaxel

The cost data reported in the three pharmacoeconomic analyses would seem to be different if one considers the absolute cost values per patient and per type of treatment, but they are instead very similar when expressed as the cost difference between the two treatments (i.e. the incremental cost per patient). In fact, the absolute data of cost per patient and per type of treatment contained different items across the three pharmacoeconomic studies. For example, Messori *et al.*[7] included only drug acquisition costs, costs for chemotherapy administration, hospitalization costs and costs for treating cases of neutropenia, whereas both McGuire *et al.*[6] and Elit *et al.*[5] adopted a much longer list of cost items. There was in fact a difference in the design of the cost analysis between these three studies. The works by Elit *et al.*[5] and by McGuire *et al.*[6] were specifically aimed at determining the values of absolute cost for the two treatments, and not only the cost difference per patient between the two treatments. In contrast, Messori *et al.*[7] explicitly stated that the objective of their study was the estimation of incremental costs (not the estimation of absolute costs per patient and per type of treatment) and so the cost items that were thought to be similar between the two treatments were disregarded. This explains why the values of absolute cost of Messori *et al.*[7] were lower than those calculated by Elit *et al.*[5] and by McGuire *et al.*,[6] and explains also the finding that the three estimates of incremental cost were, instead, very similar.

Table 5. Values of cost per life-year gained obtained from lifetime studies based on the Markov method or the Gompertz approach

Disease condition	Innovative treatment (A)	Reference treatment (B)	First author and reference	Cost per life-year gained (using A as opposed to B)	Method of survival prediction
Stage III resected colon cancer	adjuvant chemotherapy with levamisole and fluororacil	no adjuvant chemotherapy	Bonistalli[14]	$1422[b] or $1501[b] (per QALY)	Gompertz
Node-positive breast cancer	adjuvant CMF	no adjuvant chemotherapy	Messori[22] Trippoli[28]	$1505[c] or $1255[c] (per QALY)	Gompertz
Oesophageal adenocarcinoma	multimodal therapy (chemotherapy plus radiotherapy)	no adjuvant therapy	Davini[15]	$3961[c]	Gompertz
Relapsed chemosensitve non-Hodgkin's disease	autologous bone marrow transplantation	salvage chemotherapy	Messori[19]	$9229[c]	Gompertz
Non-Hodgkin's lymphoma relapsing after the first autologous transplant	second bone marrow transplant	standard chemotherapy	Messori[26]	$11111[b]	Gompertz
High-risk resected cutaneous melanoma	interferon	no adjuvant therapy	Hillner[16]	$13700[b] or $15200[b] (per QALY)	Markov
High-risk resected cutaneous melanoma	interferon	no adjuvant therapy	Messori[21 d]	$16467[c]	Gompertz
Chronic myelogenous leukaemia[d]	interferon	cytotoxic therapy	Liberato[18]	$63500[c] to $89500[c] (per QALY)	Markov
Chronic myelogenous leukaemia[d]	inteferon	busulfan or hydroxyurea	Messori[27]	$90000[c] to $220000[c]	Gompertz

[a]With no discounting in costs and survival.
[b]With 3% annual discounting for both costs and survival.
[c]With 5% annual discounting for both costs and survival.
[d]This topic is controversial;[34] there is another cost–effectiveness study published by Kattan *et al.*[17] (Markov method) that found a cost per life-year gained of $25600[c] and a cost per QALY gained of $34800[c] (discounting = 5% per year).

Our comparative overview of the three pharmacoeconomic studies on first-line paclitaxel in advanced ovarian cancer indicates that the cost-effectiveness profile of this treatment is by now rather well characterized because homogeneous results were produced by the three independent analyses. The costs per life-year gained attained a value around $20 000, which is generally considered within an acceptable range for society.

The entire premise of these three pharmacoeconomic analyses is that first-line paclitaxel improves survival to the extent observed in the GOG111 study (improvement in median survival from 24 to 38 months; improvement in median progression-free survival from 13 to 18 months[4]). In other words, one limitation of these pharmacoeconomic analyses is that they all were based on a single clinical study. Quite recently, however, the results of a clinical trial coordinated by the EORTC have confirmed that first-line paclitaxel prolongs survival in advanced ovarian cancer with an increase in median progression-free survival from 12 to 16.6 months.[9] Because this clinical result is very similar to that obtained in the GOG111 study, this EORTC trial provides further experimental support to the results of the previous cost-effectiveness analyses. The duration of paclitaxel infusion was 3 h in the EORTC trial[9] compared with 24 h in the GOG111 study;[4] hence, using the 3 h infusion scheme could result in an improvement in the cost-effectiveness profile of first-line paclitaxel because the costs of chemotherapy administration are lower. However, this hypothesis needs confirmation.

Finally, our overview of these three cost-effectiveness studies demonstrates that pharmacoeconomics has reached a sufficient degree of methodological maturity because three studies conducted independently by different research groups produced virtually the same conclusion in terms of cost per life-year gained.

Advantages in using primary data of cost and survival in pharmacoeconomic models

In a comparative analysis of these three pharmacoeconomic studies, some differences emerge in the way the various authors handled the data of cost and survival for these patients and for these treatments. McGuire *et al.*[6] directly introduced the primary cost data of their patients in their pharmacoeconomic model; hence, the information of both cost and survival was derived, in this study, from the same patient cohort. In contrast, both Messori *et al.*[7] and Elit *et al.*[5] derived, on the one hand, the survival data directly from the GOG111 study and, on the other, they obtained the cost data needed for their analyses from different sources (literature data in the case of Messori's study, local cost data in the case of Elit's study).

In general terms, the pharmacoeconomic analyses where the authors have access to the primary data of cost and survival of a single patient cohort are recognized to be more robust and more reliable.[10-12] However, our comparison of these three studies shows that the cost-effectiveness results were virtually identical both when the authors had access to the primary data of the GOG111 trial, and when the authors had no access to this information and therefore relied on alternative methods for estimating costs and survival.

The controversy of using published information (or secondary data) versus individual patient data (or primary data) has already been debated in the field of meta-analysis without the achievement of a substantial consensus.[13] The methodology of pharmacoeconomic modeling is likely to raise exactly the same problem.

Discusssion

First-line paclitaxel in advanced ovarian cancer poses a relatively easy question to researchers in the area of cost-effectiveness because simple models of analysis can be suitable for studying this issue. Our literature overview showed that the pharmacoeconomic results remain unchanged regardless of whether or not complex techniques for long-term extrapolation of survival ('lifetime techniques[7,8]) are employed.

In the vast area of cost-effectiveness studies, there is, however, an increasing consensus[10-12] that modern analyses should always be based on a lifetime approach. In this framework, the two principal methods for conducting a lifetime study include the Markov decision-tree models[10-12] and the Gompertz extrapolation technique,[8] which both have been used very often to address cost-effectiveness issues in the area of oncology.[7,14-28] Markov models rely on computer-simulated patient cohorts in whom the probability of transition between different health states (e.g. alive versus dead, maintenance of remission versus relapse, presence or absence of treatment-related side-effects, etc.) and the consequent cost estimates are derived from published information. Gompertz methods utilize a slightly different approach because they consider a very small number of clinical and economic end-points (e.g. alive, relapsed, dead)

and utilize the results reported a single clinical trial to estimate the probabilities of transition between health states. Table 5 summarizes the results of a series of recent lifetime pharmacoeconomic studies conducted in the area of oncology. The information presented in Table 5 provides a useful reference term to better interpret the cost-effectiveness results on first-line paclitaxel in advanced ovarian cancer and substantially confirm the economic attractiveness of paclitaxel treatment.

Quality of life is becoming more and more important in evaluating anti-cancer treatments[29] and consequently the cost per quality-adjusted life-year (QALY) gained is increasingly used to express the results of pharmacoeconomic studies.[10-12] As regard the use of taxanes in ovarian cancer, quality-of-life research is still at an initial stage. A simplified analysis on first-line paclitaxel[25] has been published where quality of life was stratified on three levels only (maintenance of remission, progression and presence of treatment-related toxicity in the framework of the Q-TWIST approach[30]); its results showed that first-line paclitaxel implies a favorable profile in terms of cost per QALY gained (about $18 200 per QALY gained).[25]

Docetaxel is another taxene that has been proposed for use in patients with advanced ovarian cancer.[31-33] Since this drug has not yet been approved for ovarian cancer and is not marketed for this indication, a pharmacoeconomic assessment is premature.

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