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Economic evaluation of chemotherapy

Palliative therapy in advanced ovarian cancer: balancing patient expectations, quality of life and cost

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The goals of chemotherapy for recurrent/refractory ovarian cancer are the palliation of disease-related symptoms, and improvement of quality and quantity of life. Previous studies of palliative therapy in advanced ovarian cancer have focused on surrogate measures of patient benefit rather than evaluating palliative end-points such as quality of life and clinical benefit. The impact of palliative chemotherapy on survival, quality of life and cost in advanced ovarian cancer are unknown as there have been no studies comparing palliative treatment with best supportive care. Although there is insufficient information from existing studies to determine whether palliative therapy in advanced ovarian cancer is cost-effective, there is some evidence to suggest that chemotherapy has a role in palliation of symptoms with an apparent improvement in quality of life. We relate the results of two studies. (i) A prospective study evaluating the cost of second/third-line chemotherapy as well as its effectiveness, which found the mean total cost per patient for the study period (one line of chemotherapy) was Canadian $12 500. In addition, half of patients seemed to derive some palliative benefit and a quarter of patients had an objective response in their disease. (ii) A retrospective study evaluating all costs from the initiation of palliative chemotherapy until death which demonstrated a cost of Canadian $53 000 per patient. Our studies demonstrate that patient expectations of palliative therapy in ovarian cancer are high and patients are willing to put up with significant toxicity for modest benefit. Although palliative therapy may be associated with high costs, even modest prolongation of survival can render such treatment cost-effective. The major cost saving associated with palliative therapy is from the reduced need for hospitalization towards the end of life. Future studies in recurrent/refractory ovarian cancer should focus on palliative end-points and include a comparison with best supportive care. [© 1998 Lippincott Williams & Wilkins.]

Key words: Advanced ovarian cancer, palliative therapy, patients expectations, quality of life.

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Introduction

Pharmaco-economic evaluations in medicine are important because the costs of medical care, including good quality palliation and symptom control, are high and the demand for a fixed pool of resources is continually increasing. Accurate assessments of cost and effectiveness are necessary to determine the most appropriate utilization of resources. Is it appropriate, for example, that curative treatments be given priority over palliative treatments?

In an ideal setting, the cost of health care could be overlooked and the decision to implement a specific treatment be based solely on its efficacy. Increasingly, however, costs are important and escalating. The process of assessing costs and balancing them with effectiveness has in fact evolved into a well-defined discipline which allows the comparison of disparate treatments. Costs, when divorced from treatment outcomes, are meaningless and must instead be evaluated in the context of factors such as survival and improvement in quality of life. The dollar value is only of relevance in the appropriate context. Health care decisions therefore cannot be based solely on cost; they must balance appropriate outcomes, be pragmatic and, above all, ethical.

Ovarian cancer is a disease which kills over 15 000 women every year in North America alone. The median life expectancy is short and the majority of women are diagnosed at an advanced stage, making cure unattainable for most. Thus palliative therapy in this disease is of paramount importance.

This article looks at palliative therapy of advanced ovarian cancer from the perspective of the provider as well as the consumer, asking four basic questions:

(i) What is the nature of the disease and what can treatment provide, i.e. what is for sale?
(ii) What does the patient want?
(iii) What are the true treatment related costs?
(iv) What are the alternatives?

Background

Epithelial ovarian cancer is the leading cause of death from gynecologic malignancy and accounts for 5% of all cancer-related deaths.[1] There were an estimated 29 000 new cases of epithelial ovarian cancer in North America in 1997 with 15 550 deaths.[2,3] The 5-year overall survival rate for all patients is 31.9%.[4] Approximately 70% of patients will present with advanced FIGO stage III or IV disease and despite objective response rates of 60–80% for cisplatin-based chemotherapy, the majority of patients will relapse. Only 10–20% of patients with suboptimally debulked stage III or IV disease will be alive at 5 years with a median survival duration of 24–38 months.[5,6] Disease which recurs or progresses more than 6 months after platinum-based chemotherapy may be re-treated with similar agents and reported response rates are in the range of 27–60% with a median survival duration of 1 year.[7–10] Women who recur during or less than 6 months after a cisplatin-based regimen are deemed to have cisplatin-resistant disease and have been treated with alternative agents such as paclitaxel, ifosfamide, hexamethylmelamine, oral etoposide, tamoxifen or topotecan. Response rates for such patients range from 12 to 30% with a median survival of 9 months.[11–24] Although there is no persuasive data to support a curative role for salvage therapy, the vast majority of studies of palliative chemotherapy in this group of women have focused on surrogate measures of patient benefit, such as response rate and time to progression without considering direct measures of clinical benefit, most importantly quality of life. As second-line agents are generally disappointing, the main focus of treatment for recurrent disease should be palliation. Furthermore, in an era of declining resources in all health care systems, it is important to consider the resource implications of palliative therapy through formal cost-effectiveness studies. Given the magnitude of patients who will die of progressive malignant disease, the role and resource implications of chemotherapy for recurrent and refractory ovarian cancer need to be carefully evaluated.

Palliative therapy for recurrent/ refractory ovarian cancer

When evaluating the role of palliative chemotherapy for recurrent/refractory ovarian cancer, it is particularly important to establish the goals of such treatment as well as define the relevant outcomes. In the absence of any curative benefit of palliative therapy, its main focus should be the amelioration of disease-related symptoms. There is an inherent expectation by many patients that palliative chemotherapy for advanced ovarian cancer may prolong quantity of life. If this

Table 1. Second-line agents in recurrent ovarian cancer

Agent	Comments
Cisplatin-based chemotherapy	platinum-free interval (PFI) > 24 months: RR 59%[19] PFI 13–24 months: RR 33% PFI 5–12 months: RR 27% primary platinum refractory: minimal RR
Non-platinum chemotherapy	
Paclitaxel	20–40% RR in phase II studies[12,21–23] 22% RR in NCI study of women failing ⩾3 lines of chemotherapy median survival 9 months
Ifosfamide	10–20% RR in phase II studies[13,14] active in cyclophosphamide-treated patients; non-cross-resistant possible future role, given increased use of first-line paclitaxel and cisplatin
Topotecan	overall RR 20.5%[18] RR for platinum-resistant disease 13.3%
Hexamethylmelamine (oral)	10–15% RR[15–17] activity in true platinum-refractory disease not established
Etoposide (oral)	10–20% RR in phase II studies[19,20] well-tolerated
Tamoxifen	objective RR 17%, CR 7% in phase II study of Mid-Atlantic Oncology Program[24] minimal toxicity

were to occur, there should be a parallel improvement in quality of life. The value of systemic therapy in second- and subsequent-line treatment of advanced ovarian cancer has been explored with many phase II and III studies; however, none have looked primarily at quality of life or clinical benefit. The various agents used for recurrent/refractory ovarian cancer are summarized in Table 1.

Quality of life in recurrent/ refractory ovarian cancer

Quality of life involves the evaluation of multiple dimensions including physical, functional, psychological and social parameters, and assesses an individual's satisfaction with their current health state. Although evaluation of quality of life has in the past been considered 'subjective' and has faced methodological challenges, the instruments available for its assessment have been scrutinized in a rigorous scientific manner. While they are subjective in that they assess individual patient opinion, quality of life analyses have demonstrated validity, reliability and sensitivity in formal evaluations.[25]

The inclusion of quality of life assessments in trials of palliative therapy for ovarian cancer are particularly meaningful, given that any agent will have little impact on survival but has the potential to cause significant toxicity. However, few studies have evaluated the effects of palliative chemotherapy on quality of life in patients with ovarian cancer.

In view of the known toxicity of palliative chemotherapy, its comparison with best supportive care remains an intriguing question in ovarian cancer and merits further investigation. In a similar context, Tannock *et al.* have evaluated palliative therapy for hormone-resistant prostate cancer, comparing mitoxantrone and prednisone with prednisone alone. This study evaluated the palliative benefit of chemotherapy using validated scales for pain and quality of life. The primary end-point was a palliative response of a two-point reduction in pain on a six-point scale with the assessment made by patients. Secondary end-points were a reduction of greater than or equal to 50% in analgesic medication use without increase in pain, duration of response and survival. Quality of life was measured using linear analog self-assessment scales, the EORTC core questionnaire and a disease-specific module. Thirty-eight percent of patients receiving mitoxantrone and prednisone fulfilled criteria for primary or secondary palliative end-points, while this was seen for 21.1% of patients on the prednisone alone arm (p=0.025). Median duration of palliative response was 43 weeks for mitoxantrone and prednisone, and 18 weeks for prednisone alone.[26] This study demonstrated the significant palliative advantage of chemotherapy in symptom control in this setting.

Burris *et al.* have also evaluated clinical benefit of gemcitabine in patients with advanced pancreatic cancer in a randomized trial, with 5-fluorouracil (5-FU) as a control arm. The assessment of clinical benefit was based on the evaluation of pain (analgesic consumption and pain intensity), functional impairment (Karnofsky performance status) and weight loss. Clinical benefit required a sustained ($\geq$4 weeks) improvement in at least one parameter without worsening in any others and was seen in 23.8% of gemcitabine-treated patients compared with 4.8% of 5-FU-treated patients (p=0.0022).[27]

Well-designed, randomized palliative trials in the area of ovarian cancer are necessary in order to fully evaluate the role of palliative therapy. Montazeri *et al.* performed a literature search through MEDLINE and of published papers on quality of life in patients with ovarian cancer from 1976 to 1994. The MEDLINE search disclosed 48 citations, of which 36 made only a passing reference to quality of life in their abstracts. Twelve papers dealt with measurement of quality of life, with 10 of these being in English, one in Dutch and one in German.[28] De Haes *et al.* measured quality of life, in patients with advanced ovarian cancer randomized to either HEX-CAF or CHAP-5 combination regimens. Although the CHAP-5 regimen appeared more toxic than the HEX-CAF regimen, the overall quality of life analysis did not show significant differences between either treatment.[29]

In a more recent prospective study by our group, patients undergoing second- or third-line palliative chemotherapy for advanced ovarian cancer were assessed to evaluate palliative benefit of conventional therapy.[30] Patients with histologically confirmed epithelial ovarian cancer who had previously received first-line therapy with a cisplatin- or carboplatin-based chemotherapeutic regimen were entered in the study if they were about to start second- or third-line chemotherapy for progressive or recurrent disease.

In order to evaluate patients' expectations, an in-house questionnaire was administered at baseline, before starting the first cycle of chemotherapy. Before completing the questionnaire, patients had met with their physician who explained that the primary goal of chemotherapy would be to palliate symptoms. Patients were also told that chemotherapy in this setting was not curative. Patients were asked if they thought that chemotherapy would make them feel better, delay further problems, make them live longer, cure their

disease or make them feel worse. The potential responses were in the form of a four-point scale: not at all, a little, quite a bit or very much. They were also asked: overall how do you think chemotherapy will make you feel? The response was in the form of a seven-point scale ranging from much worse to much better. Patients were also asked if they thought that chemotherapy would be very, moderately, a little or not worthwhile. This last question was asked at baseline and repeated after completion of chemotherapy.

The EORTC quality of life C-30 core questionnaire and the FACT-O (ovarian) questionnaire were used for measurement of quality of life in this study. Any increase in score from cycle 2 compared to baseline was considered as an improvement. It was assumed that if the quality of life improved in less than 20% of patients, the chemotherapy would be considered not worthwhile to improve quality of life. Duration of survival was measured from time of entry in the study using the Kaplan–Meier method. A sensitivity analysis was performed to assess the impact of changes in the cost of individual categories on total cost. The percentage of change in the cost of each category that would be required to change total cost by 1% was calculated.

Twenty-seven eligible patients commenced second- or third-line chemotherapy between July 1994 and October 1996. All women had received carboplatin- or cisplatin-based chemotherapy previously. The majority of women were entered on study on the second line of chemotherapy. Carboplatin- or cisplatin-based regimens and paclitaxel were the most frequently prescribed treatments. Patients received a median of three cycles. Of the 26 patients evaluable for response, the response rate was 27% (seven of 26); three had a complete response (12%) and four had a partial response (15%). Fourteen patients had progressive disease. The median survival from entry into the study was 11 months.

Patients' expectations regarding chemotherapy were as follows: the majority of women expected that chemotherapy would make them feel better (58% quite a bit/very much), would delay further problems (62%) and make them live longer (65%). Interestingly, 42% thought that chemotherapy would have a moderately high to high likelihood of curing their disease. Only a few patients expected they would feel worse (quite worse or much worse). All women thought chemotherapy would be at least moderately worthwhile at entry into the study (three who did not answer). After the end of treatment women were asked if they felt chemotherapy had been worthwhile. Of the 11 women who answered, five felt it was very worthwhile, one moderately worthwhile, two little worthwhile and three that it was not worthwhile. Of those who answered very or moderately worthwhile all had had a partial or a complete response. Those who answered this was not worthwhile had either stable or progressive disease.

There were 21 patients who completed two cycles of chemotherapy and either had the third cycle or a follow-up visit and were available for quantitative assessment of a change in quality of life scores at cycle 2 compared with baseline. After two cycles of therapy there was improvement in some of the domains, particularly emotional function and global health. Improvement in symptom control, particularly pain and nausea and vomiting, was also apparent in over half of the patients.

The most striking results were in sustained improvement in emotional and global health status/quality of life subclass of the EORTC questionnaire with improvement lasting from 2 to more than 3 months. The symptom control seemed also quite good particularly for pain control with improvement in 52% of patients for a median of 54 days. Again, emotional function was the domain where most of the patients (65%) had a sustained improvement for a median of 97 days.

This study provides insight into patient expectations and emphasizes the need to objectively study palliative benefit using validated quality of life instruments. It is apparent from this study that patients expect to benefit from palliative chemotherapy and they do indeed derive palliative benefit, although improvements in global function may not correlate with traditional outcome measures.

Costs—the economics of palliative therapy in ovarian cancer

The increasingly limited resources in health care are resulting in a greater degree of scrutiny of the costs of cancer care. Economic evaluations involve a comparative assessment of two or more alternative courses of action in terms of both their costs and consequences.[31] To date, in the field of oncology, most economic evaluations have focused on interventions which have curative potential, including adjuvant chemotherapy for breast cancer and have used endpoints such as cost per life-year gained.[32]

There have been only a limited number of studies evaluating the cost of palliative chemotherapy and palliative care. There are several types of costing studies which can be performed and they include:[33]

- *Cost-minimization.* When good data prove that two interventions have the same outcome, only

the difference in costs is compared.

- *Cost-utility analysis.* Allows different health outcomes (mortality and morbidity) to be compared. Life-years gained are adjusted for quality of each life-year, using a measure called 'quality-adjusted life-years' (QALYs).
- *Cost-benefit analysis.* Assesses whether a program has net benefits over the next-best alternative. All costs and benefits must be valued in monetary terms and this often relies on valuing changes in productivity.
- *Cost-effectiveness analysis.* Allows comparison of alternatives in which both the costs and outcomes differ. The result is expressed as a cost-effectiveness ratio of the net resource costs of an intervention to the net benefits or the cost per unit outcome and is ideally suited for evaluation of palliative therapies.

However, costing studies, particularly those based on randomized control trials, are difficult to do, especially if they involve a control arm of best supportive care. There have been no such studies to date in advanced ovarian cancer. We decided to look at the costs of palliative care in two different studies: (i) a prospective study evaluating the cost of second/third-line chemotherapy as well as its effectiveness and (ii) a retrospective study evaluating all costs from the initiation of palliative chemotherapy until death.

Prospective study evaluating cost of second/third-line chemotherapy

Methods. In this prospective study described earlier by Doyle *et al.* of women undergoing second- or third-line chemotherapy, resources used in patient treatment were recorded prospectively.[30] Attributable costs were calculated at the end of the study and determined in 1994 Canadian $ (US$1.00 ≈ Canadian $1.40) and were reported rounded to the nearest $100. Costs were divided into the following major categories: in-patient, out-patient, chemotherapy drugs, non-chemotherapy drugs, radiotherapy, laboratory tests and diagnostic imaging. The costing period extended from the entry into the study until the end of study date, i.e. two follow-up visits after completion of chemotherapy. The hotel-approximation method described by Hull *et al.* was used.[34,35] This method makes the assumption that certain 'hotel' costs are the same for each in-patient day or each out-patient visit independent of the reason for admission or for visit. The costs of administration, housekeeping, security, laundry, nutrition, medical records and maintenance fall into this category. The proportion of these hotel costs attributable to in-patient as compared to out-patient services was estimated using an appropriate allocation unit for each item based on the 1994 fiscal year financial report. To these hotel costs were added the individualized costs of medical care for each patient including nursing, ward supply, physician services and special procedures.

The costs of laboratory tests and diagnostic imaging were calculated from the Ontario Health Insurance Plan Fee Schedule which provides a unit system that takes physician fee, technician time and other costs into account. The costs of drugs prescribed were based on the cost to the hospital of purchasing the drugs using a computerized data base and price lists. The costs of preparation by the pharmacy staff based on average preparation time and salaries were added. The hotel approximation method was also used including salaries of staff involved in direct patient care, professional fees and salaries of radiation oncologists, salaries of support and technical staff, costs of supplies, and depreciation cost of major equipment.

The mean number of outpatient visits was 6.4 (range 2–13), the mean number of hospital admissions was 1.1 (range 0–7) and the mean number of in-patient days per patient was 7 (range 0–36). Seventy percent of in-patient days were for symptomatic care in the context of progressive disease. Delivery of chemotherapy as the main reason for admission accounted for 24% of in-patient days and complications of chemotherapy represented 4% of in-patient days.

Outcome. The mean total cost per patient for the study period (one line of chemotherapy) was $12 500. In-patient admissions accounted for 37% of total costs while out-patient visits made up for 16% of total costs. Chemotherapy drug cost accounted for 37% of total costs. When adding other costs associated with chemotherapy such as in-patient days for chemotherapy delivery or complications, chemotherapy related costs become substantially higher and accounted for 46% of total costs. Other components accounted for only a small proportion of total costs.

Retrospective study evaluating cost of palliation from initiation of second/third-line chemotherapy to death

This was a retrospective evaluation of the resource implications of palliative chemotherapy in ovarian

cancer.[32] The purpose of this study was to describe the costs and outcomes of palliative chemotherapy from initiation of treatment until death, in women with recurrent and refractory ovarian cancer from the perspective of a health care provider.

Methods. This was a retrospective study of 40 consecutive women who started second- or third-line chemotherapy for recurrent or refractory ovarian cancer between 1989 and 1992 at the Princess Margaret Hospital (PMH). Resource utilization from the commencement of second- or third-line chemotherapy until death or last follow-up was determined from a detailed chart review. All elements of care were recorded, including in-patient admissions, out-patient visits, chemotherapy drugs, non-chemotherapy drugs, radiation therapy, surgical procedures, investigations and homecare. Costs were calculated using the hotel approximation method and are expressed in 1994 Canadian $. Actuarial estimates of cost and survival were used to account for censored observations.

Costs were calculated from the day that the decision was made to start second- or third-line chemotherapy until death. Information was retrieved from medical records: detailed description of all subsequent treatment including surgery, radiotherapy, chemotherapy or hormonal therapy; the number and duration of in-patient admissions with the principal cause for each hospitalization; the number of out-patient visits to surgeons, medical oncologists, radiation oncologists and other physicians distinguishing between chemotherapy and non-chemotherapy visits; all laboratory and radiological investigations; date, cause and place of death. When available, data on use of homecare was recorded. The doses of all chemotherapy and non-chemotherapy drugs dispensed to each patient by the PMH pharmacy were extracted from a computer database.

Costs were divided into the following major categories: in-patient, out-patient, chemotherapy drugs, non-chemotherapy drugs, radiotherapy, laboratory tests, diagnostic imaging and home care. Costs were calculated according to 1994 values, in Canadian $ (US$1.0 ≈ Canadian $1.4), and are reported rounded to the nearest $100.

The cost of each laboratory and imaging test was calculated from the Ontario Health Insurance Plan Fee Schedule which provides a unit system that takes the physician fee, the technician time and other costs into account. When a test not available at PMH was performed at another hospital, the amount charged to PMH by the other hospital was used.

The costs of drugs prescribed by PMH physicians was based on the cost to the hospital of purchasing the drugs. The data come from a computerized database which includes the cost of all drugs provided by the pharmacy department of PMH. To these costs were added the costs of preparation by pharmacy staff based on average preparation times and salaries.

Kaplan-Meier product-limit estimates were calculated for survival times and costs; medians and means were derived directly from the curves. The relationship between cost and survival was explored graphically and with censored linear regression.[36] Survival times were calculated from the dates of: (i) first diagnosis of ovarian cancer, (ii) first relapse, (iii) start of costing, and (iv) the start of first-, second- and third-line chemotherapy.

A sensitivity analysis was performed to assess the impact on total costs of changes in the cost of individual categories. The percentage change in the cost of each category that would be required to change the total cost by 1% was calculated.

Table 2. Distribution of the overall costs of care: actuarial

Category	Cost (Canadian $)			Percent of total	Percent changed needed to change the total by 1%
	Mean	Median	Range		
In-patient admissions	32749	22933	0–117811	62	1.6
Out-patient visits	4270	3573	262–13686	8	12
Chemotherapy drugs	11182	6387	190–37528	21	5
Other drugs	742	247	11–4898	1.4	71
Laboratory tests	1915	1751	390–6648	3.6	28
Imaging studies	1461	1253	56–5660	2.8	36
Radiation therapy	323	0	0–1835	0.6	163
Home care	1036	0	0–10292	2.0	51
Total	52960	36611	4831–162897	100	

Outcomes. After a minimum follow-up period of 24 months, 36 of the 40 women had died. The median survival of the group was 1.1 years from study entry and 1.7 years from first relapse. The women received a median of two regimens of chemotherapy (range 1–4) from study entry. They spent a median of 33 days as hospital in-patients (mean 46; range 0–185); 58% of these in-patient days were for symptomatic management and 32% were for chemotherapy. The actuarial estimate of the mean cost per patient was $53 000. The breakdown of total costs is summarized in Table 2. In-patient admissions accounted for *61%* of total costs while out-patient visits accounted for only 8% of the total costs. Chemotherapy drug costs accounted for *21%* of total costs; however, the total costs associated with chemotherapy were substantially higher. If the costs of in-patient days for chemotherapy drug delivery, in-patient days for treatment of complications and out-patient visits related to chemotherapy were included then chemotherapy-related costs accounted for *45%* of the total cost (see Table 3). Costs attributable to supportive care, such as those for in-patient admissions for terminal care, non-chemotherapy drugs and palliative radiation therapy, accounted for about 43% of the total costs. Other components accounted for only a small proportion of the total costs.

The sensitivity analysis summarized in column 5 of Table 2 shows the increase in the cost of an individual category required to increase the total cost by 1%. For example, an increase of either 5% in the cost of chemotherapy drugs or 1.6% in the cost of in-patient care would result in an increase of 1% in the total cost. Thus the estimate of total costs is most sensitive to those categories which account for the greatest proportion of total costs, such as in-patient admissions and chemotherapy, and is least sensitive to those accounting for the smallest proportion, such as radiation therapy.

The relationship between cost and survival duration was not linear: the cost per year depended on the survival duration. This made the cost per year a poor summary of the data. The interpretation is that the cost per year is highest for those who live the shortest time. Thus a 100% increase in survival duration is associated with only a 50% increase in costs and a 50% reduction in survival duration is associated with only a 33% reduction in costs (see Table 4).

Discussion

How does palliative therapy of ovarian cancer compare with other treatments and can we as a society afford it? The costs associated with various malignant and non-malignant diseases have been evaluated, and are summarized in Table 5. Other areas where economic evaluations have been performed for palliative therapy include lung and prostate cancer. There have been two complete economic evaluations in the area of palliative therapy for lung cancer by the National Cancer Institute of Canada (NCIC).[37,38] One of these trials involved patients with extensive small cell lung cancer randomized to CAV (cyclophosphamide, adriamycin and vincristine) or CAV alternating with VP-16 and cisplatin. Survival was increased by 1.6 months in the alternating therapy arm and the additional cost of this treatment (including all costs from randomization to death) was $450 per patient (1984 Canadian $).[37] The second study by the NCIC involved patients with unresectable non-small cell lung cancer who were randomized to receive CAP (cyclophosphamide, adriamycin and cisplatin), VP (vindesine and cisplatin) or BSC. Patients receiving

Table 4. Relationship between survival time and cost

Difference in survival time (%)	Difference in cost (%)
+200	+90
+100	+50
+50	+27
−50	−33
−75	−55

Table 3. Costs attributable to chemotherapy and supportive care (Canadian $): actuarial

Category	Chemotherapy	Supportive care	Uncategorized	Row total	Percent total
Drug costs	11182	742		11924	22
In-patient costs	11462	18994	2293	32749	61
Out-patient costs	1366	2904		4270	8
Other		323	4412	4735	9
Column total	24010	22963	6705	53678	100
Percent total	45	43	12	100	

Table 5. Cost associated with treatment of various malignant and non-malignant conditions

Adjuvant therapy for breast cancer	$30000 per QALY[40]
First-line chemotherapy for advanced ovarian cancer	$50054 lifetime cost per patient[41]
Palliative chemotherapy for non-small cell lung cancer	−$6172 per year of life gained[38]
Palliative chemotherapy for prostate cancer	$26500 per patient[39]
Palliative therapy for advanced breast cancer	$18600 per patient[42]
Palliative chemotherapy for ovarian cancer	
costs of chemotherapy	Canadian $12500[30]
cost from start of chemotherapy until death	Canadian $53000 per patient[32]
Hospital-based hemodialysis	$48700 per year of life gained[43]
Terminal care	US$56–62000[45]

chemotherapy had prolongation of median survival compared to BSC (12.4 weeks for VP and 8.0 weeks for CAP). A cost-effectiveness analysis demonstrated that the use of CAP resulted in a savings of $949 (1984 Canadian $) per patient or $6172 per year of life gained. The use of VP resulted in an additional cost of $3638 per patient or $14 778 per year of life gained. The conclusion of cost savings and prolonged survival with CAP compared with BSC related to the decreased need for hospitalization in patients receiving chemotherapy.[38]

Cost-effectiveness has also recently been evaluated in patients receiving either prednisone alone or prednisone plus mitoxantrone in a randomized trial to evaluate the palliative treatment of hormone-resistant prostate cancer (HRPC). In this study, 161 patients with symptomatic HRPC were randomized to either prednisone alone or prednisone plus chemotherapy and a palliative benefit was seen for the chemotherapy arm (median duration 11 months). Utilization of resources was documented from trial entry until death. The results from an initial cost analysis of 33 patients entered at PMH showed a median total cost from randomization to death of Canadian $26 500 for the chemotherapy arm and $30 500 for the prednisone only arm. Cross-over from prednisone alone to mitoxantrone plus prednisone was allowed if there was no response and the cost of patients who received prednisone only was $29 000. The mean palliative response was 19 days for prednisone alone and 94 days for mitoxantrone plus prednisone. The preliminary data thus showed the use of mitoxantrone plus prednisone was a cost-effective strategy in the palliative treatment of HRPC.[39]

The cost associated with end of life treatment has been demonstrated to increase exponentially as death approaches.[44,45] Although palliative chemotherapy may appear to add to these costs, it is apparent from selected economic evaluations that there may in fact be cost savings associated with the reduced need for hospitalization in patients treated with chemotherapy. Furthermore, the clinical benefits of chemotherapy have recently been validated in several tumor types through well designed trials using palliative endpoints. The cost of palliative chemotherapy *per se* for ovarian cancer is relatively modest, at Canadian $12 500 (US$9000) on average, with approximately half of patients seeming to derive some improvement in quality of life and one-quarter of patients responding objectively. The main component of cost is end of life care and hospitalization, as demonstrated in the prospective study by Doyle *et al.* The balance of cost and clinical benefit may therefore favor palliative chemotherapy; however, an estimate of the cost-effectiveness of palliative chemotherapy for ovarian cancer will require an assessment of the costs associated with BSC alone.

A large proportion of costs associated with palliative therapy are related to hospitalization and terminal care. Emanuel and Emanuel looked at the economics of dying, reporting the average hospital cost for dying patients to range between US$56 000 and $62 000, depending upon whether patients had an advance directive or not. However, they felt that it would be difficult to substantially reduce the percentage of health care expenditure in patients who did have an advance directive because humane care at the end of life is labor intensive and therefore expensive.[45]

Our experience and other studies at PMH would tend to support this view. Palliative chemotherapy does palliate and the cost of doing so is not unreasonable. However, it is evident that chemotherapy-related costs begin to escalate with multiple lines of therapy. It is likely that with repeated regimens of chemotherapy, the outcome may follow the law of diminishing returns.

The costs associated with terminal care are high. Optimal utilization of resources from a health care perspective would dictate supportive palliative/terminal care in the patient's home with reduction in hospitalization. There may also be major differences in costs in patients admitted for terminal care to a

hospice compared to an acute-care hospital or tertiary cancer center.

Conclusions

The goals of palliative chemotherapy in advanced ovarian cancer are to improve quality and quantity of life. Previous studies of palliative therapy have focused on surrogate end-points of patient benefit rather than direct measures of palliation. There have been no studies in advanced ovarian cancer comparing palliative chemotherapy with best supportive care, and thus the impact of chemotherapy on survival, quality of life and cost are mostly unknown. Although there is insufficient information from existing studies to determine whether palliative therapy in advanced ovarian cancer is cost-effective, there is some evidence to suggest that chemotherapy has a definite role in palliation of symptoms with an apparent improvement in quality of life. The available data from our studies would indicate that chemotherapy itself contributes only modestly to overall cost, with the large proportion of cost being incurred as a result of complications and hospitalization occurring at the end of life. Our prospective study would indicate that patient expectations of palliative therapy in ovarian cancer are high and that patients are willing to accept significant toxicity for modest benefit. How do these preferences compare with societal expectations? Slevin *et al.*[46] have shown that patients are willing to undergo aggressive therapy for modest gain. In contrast, the majority of respondents from the normal controls or health care professionals would not. Who then should make these choices? Is it even fair or ethical to do so? Community expectations of therapy may be at odds with those of patients for reasons other than cost. There is a significant shift in the frame of reference in the transition from wellness to illness. This would perhaps seem to pose a barrier to the implementation of economic health care policy if it were not for two important caveats. The appropriate assessment of cost-effectiveness in any health care area has to be ethical, and this has been outlined in the recommendations of the Panel on Cost-Effectiveness in Health and Medicine.[47] The second is more pragmatic and entails the cost of good quality care at the end of life which is recognized to be high. At present, it is unclear as to whether palliative chemotherapy will result in a net saving or add to these costs. It is apparent that although current palliative therapies are associated with high costs, even modest prolongation of survival can render such treatment cost-effective. Palliative therapy may also reduce overall costs by improving performance status and quality of life, thus decreasing the need for hospitalization.

Future studies in recurrent/refractory ovarian cancer require the inclusion of palliative end-points as well as cost-effectiveness analyses, and ideally a comparison with best supportive care to improve upon the current state of knowledge and create guidelines for the treatment of such patients.

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