ARTICLE

Time to post-op chemotherapy for ovarian cancer: one year at an Auckland tertiary centre

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INTRODUCTION

Epithelial ovarian cancer is currently ranked fifth for incidence and forth for mortality among all cancer sites for females in New Zealand (after breast, colorectal and lung). Among reproductive cancers it ranks second only to breast cancer.[1] Treatment is surgery with adjuvant chemotherapy depending on surgical stage and type of tumour.[7] Tumour resection should be radical and include total abdominal hysterectomy, bilateral salpingo-oophorectomy and omentectomy.[8,9]

The process of referral of patients for surgery and chemotherapy for ovarian cancer is relatively streamlined at National Womens' Hospital (NWH). A patient is referred to the Gynae-oncology outpatients clinic after having been through the appropriate channels and undergone diagnostic imaging (*e.g.* pelvic CT). They are then given a date for surgery if this is needed and, depending on histopathology and staging of samples obtained intraoperatively, they are referred on to the medical oncology service for adjuvant chemotherapy treatment, with CA125 monitoring. CA125 is a plasma tumour marker, the levels of which are used to detect ovarian cancer recurrence. Often individual cases are discussed in multidisciplinary meetings before this process occurs. This length of this process in some cases raises some questions regarding the fluency of referral of patients through the system. For the purposes of this retrospective study I decided to focus on one part of this referral process: the time from surgery to chemotherapy.

The aim of this retrospective study was to determine whether patients diagnosed with epithelial ovarian cancer in a large tertiary centre in Auckland (NWH) were receiving the appropriate treatment, *i.e.* post-op adjuvant chemotherapy, in a timely manner.

METHODS

Data was collected on all patients who underwent surgery for ovarian cancer between January 1st and December 31st 2003 at National Womens' Hospital in Auckland. The records of all the patients who had had surgery for ovarian cancer during that time were retrieved from the Medical Records Department at NWH. Fifty files were manually sorted through to find patients that had a documented decision to proceed with chemotherapy. This process yielded a total of 20 files.

These documents were then carefully analyzed with the incorporation of data retrieved from the various Auckland City Hospital electronic databases (namely CRIS, Concerto and Agfaweb1000) to obtain the following fields of data: Name, NHI number, Age, Cancer type, Stage, Operation date, Chemotherapy start date, Chemotherapy end date, Regimen, Post-therapy imaging date, and imaging result. The main focus was the calculated difference between the chemotherapy start date and the operation date, which yielded the Time to Chemotherapy field.

No international or national protocols exist that comprehensively outline any useful guidelines on administering chemotherapy.[5] The protocol being followed by GOG-182 (the latest ongoing chemotherapy trial by the gynaecological oncology group) states a maximum time to chemotherapy of 12 weeks (84 days).[9] After discussions with specialists, both in Gynae-oncology and Medical Oncology, at NWH, it became clear that standards for the acceptable timeframe for chemotherapy administration are anecdotal at best, and not evidence based due to the lack of studies dealing with this subject. The generally accepted rule, however, was to administer chemotherapy as soon as possible, but within 4 weeks as a rule of thumb. This was also the standard quoted by Berek.[2] The time between surgery and chemotherapy was calculated and compared to a generally accepted standard of 4 weeks.

RESULTS

Data

The complete data set is presented in the appendix (page 23). The timeframe for the administration of chemotherapy at NWH for the 18 patients with complete files is presented in Figure 1.

Comparison against the standard

For the 18 patients that had documented chemotherapy:

- Average time to chemotherapy: 63.7 days
- No. of patients receiving chemotherapy within 4 weeks: 2
- Percentage receiving chemotherapy within 4 weeks: 11%
- Percentage receiving chemotherapy within 8 weeks: 61%
- Percentage receiving chemotherapy within 12 weeks: 83%

Time trend

Another interesting and unexpected finding is the appreciable temporal trend in the data. By plotting the data sequentially as displayed in the run chart in Figure 2, the time trend becomes clearly visible (the heavy dashed line). The grey dash-dot line shows the accepted standard of 4 weeks

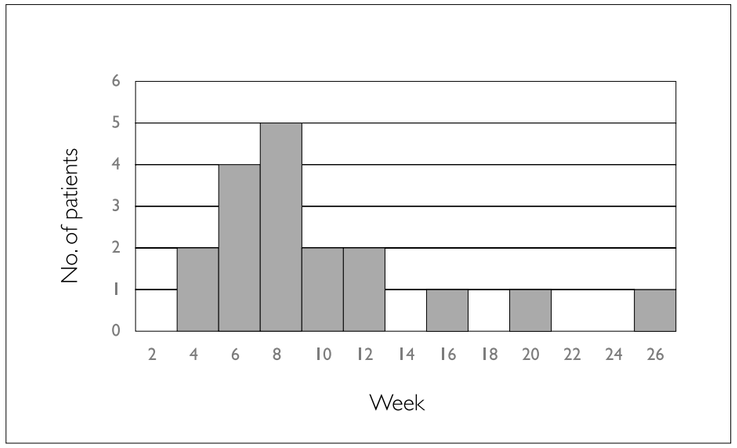

Figure 1: Time to Chemotherapy for Ovarian Cancer at National Womens' Hospital 2003

(28 days), while the grey dotted line shows the median value of the days to chemotherapy for all 18 patients (53.5 days - note that this is more representative than the mean value). Prior to June 2003, all the patients were treated in less than 53.5 days, whereas this is not the case for the rest of the year. In fact, the average time from Jan to May is 37 days (still higher than the standard), whereas the average from June to Dec is an unexpectedly high 85 days.

Statistically the 18 useful data points on the run chart above, 7 or more data points in a run indicate a special cause.[4] This holds true for the segment of the chart from Jan to May 2003, where there are 8 data points below the median. This also almost applies to the period between September and December 2003 where there are 6 points above the median, especially considering that there are two patients, not included in the run chart, that were operated on in 15/10/03 and 19/11/03 that have not yet received chemotherapy (see appendix).

DISCUSSION

Only 11% of the 18 patients received chemotherapy within the standard accepted by medical oncologists and gynaecologists at NWH. In practice, chemotherapy pre-discharge after surgery would not be feasible, if only because of delayed wound healing. Also a 100% compliance rate with the 4 week standard would probably be impossible, since on occasion there are certain issues that force a delay in treatment, such as operative complications, patient indecisiveness about chemotherapy, and even patient death. However, even bearing in mind these factors, a compliance rate of 50-75% should still be achievable. Furthermore, 83% of patients received chemotherapy within the maximum time of 12 weeks quoted by the GOG-182 protocol. Since this is regarded as a finite maximum, a compliance rate closer to 100% percent was expected. As for the post-June time prolongation, it became apparent, on further inquiry, that the medical oncology department began experiencing some staff shortage issues in June of last year. This is undoubtedly one contributor to the special cause.

Impact

The aim of post-op adjuvant chemotherapy is to deal with any residual malignant cells that could not be removed at the time of surgery. It affords a small chance of cure, and a moderate prolongation of life expectancy. Furthermore, there is data from animal tumours showing post-op acceleration and tumour proliferation for a limited time, which potentially provides a window of opportunity for adjuvant chemotherapy to act optimally. [2,6]

Delayed chemotherapy has a two-pronged effect on the patient:

- Psychological: the patient remains affected by the diagnosis for longer, and is forced to once again deal with difficult issues sometimes several months after the operation is over.

- Physical: prolonged delay in chemotherapy post-operatively gives the neoplastic cells a chance to reorganize and the 'tumour burden' to increase. The effect is four-fold:[2]

  - An overall larger number of cells to kill. Since a constant proportion of tumour cells are destroyed with each chemotherapy treatment (fractional kill hypothesis), this necessitates a longer exposure to chemo.

  - This longer exposure gives the cells a chance to become resistant to chemotherapy.

  - Larger tumours tend to have areas of low vascularity, which are less responsive.

  - Larger tumours have a smaller growth fraction (since some cells become less active) also making them less responsive to chemotherapy.

The net effect is basically a lower response rate, a higher chance of recurrence, and increased mortality rates. The author attempted to collect data on recurrence and mortality for the 18 patients but, even though followup CA125 levels were easily obtainable for all the patients electronically, the information on post-chemo imaging was scant (as can be seen in the appendix).

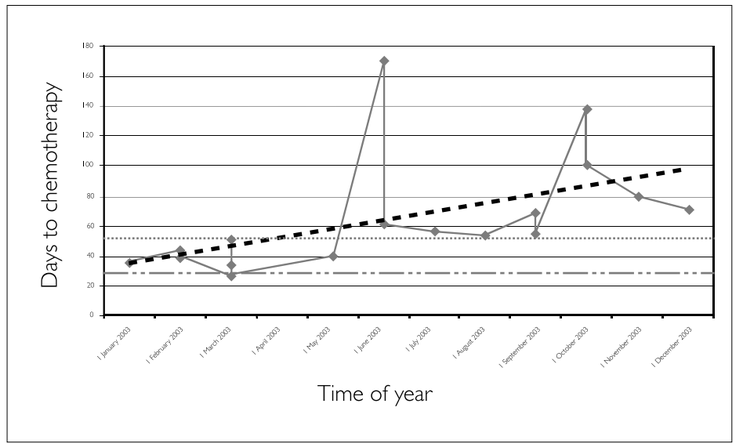

Figure 2:
Time trend: note the increase in time until ovarian chemotherapy treatment at National Womens' Hospital 2003.

Ideas for improvement

As far as improving the current situation, the ultimate aim would be to increase the percentage of patients receiving chemotherapy within four weeks. Some suggestions are:

- Implementing solutions to infrastructural deficiencies such as:

  - Remedying the shortage of specialist gynaecology pathologists, (in the few weeks preceding the writing of this report, more than two Gynae-oncology MDMs at National Womens' had to be cancelled due to the lack of the presence of a specialist Gynae-pathologist. Eventually a private practicing pathologist was employed for this purpose).

  - Reversing the shortage of medical oncology staff.

- Making the treatment delivery process more efficient by formulating care pathways and training underutilized staff, *e.g.* training ward nursing staff to administer chemotherapy, providing a care coordinator to help streamline chemotherapy assessment and treatment.

- Reducing the number of patients lost to follow-up. This is especially important since two patients who were to proceed to chemotherapy in late 2003 had no documentation of this ever happening or the reasons why. This requires:

  - Better documentation mechanisms as a method of liaison between the medical oncology and Gynae-oncology departments.

  - A monitoring mechanism. This could take the form of a computer tracking system that displays an alert when a patient due to receive chemotherapy is delayed for longer than a set time.

- Better patient advice and counselling in order to better educate the patient, and reduce indecisiveness about chemotherapy treatment.

Study Weaknesses

There are significant weaknesses in this study. The first of which is the small numbers included, and further analysis, perhaps continuing data collection into 2004, would help to improve the power of the results obtained. More extensive investigation of the causes of the worsening trend is also needed, and continuing the data collection would show whether the trend continues or perhaps even repeats (if the cause turns out to be seasonal). This study is also subject to the weaknesses of being a retrospective trial, namely in the inherent bias in data collection.

CONCLUSIONS

The net effect of delayed chemotherapy is a lower response rate, a higher chance of recurrence, and thus, increased mortality rates. It would be prudent to discover exactly what the causes of the worsening trend were. Also, continuing the data collection further (into 2004) will allow us to find out whether the trend continues. This would go some way to perhaps improving the current situation, with the ultimate aim being to increase the percentage of patients receiving chemotherapy within 4 weeks.

Acknowledgments

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Facing page images

Left: invoice for medical equipment, for NZ Presbyterian Mission Hospital in Kong Chuen, China. Dated 18/11/1924.

Top right: equipment from the Chinese mission

Bottom right: instruments from the Crimean War. Probably used for small amputations. This piece was donated by D. Wishart, who was based at East Taieri in 1854.

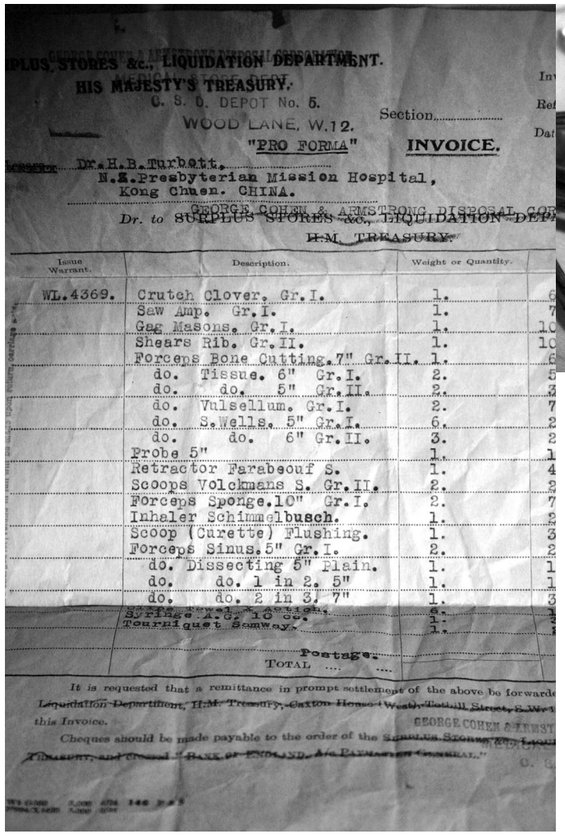
Images and equipment courtesy of Professor Pat Molloy and museum curator Bridget Inder, Research Area of Hercus Building, Otago University School of Medicine

Appendix

PATIENT	AGE	CA TYPE	STAGE	OPERATION DATE	CHEMO START DATE	CHEMO END DATE	TIME TO CHEMO	REGIMEN	IMAGING DATE	IMAGING RESULT
1	66	Endometroid	2B	21/01/2003	27/02/2003	NA	36	C/P	8/04/2003	NRD (but paraortic node)
2	73	Serous (papillary)	4	18/02/2003	1/04/2003	NA	43	C	No	
3	70	Serous (borderline)	3C	24/02/2003	3/04/2003	Passed away	39	C	18/06/2003	Recurrence
4	58	Serous (papillary)	3C	5/03/2003	1/04/2003	29/07/2003	26	C/E/P	10/06/2003	Recurrence
5	61	Serous (papillary)	3	12/03/2003	16/04/2003	19/09/2004	34	C	No	
6	84	Carcinosarcoma	2C	18/03/2003	8/05/2003	16/10/2003	50	C	No	
7	60	Serous (papillary)	4	19/03/2003	16/04/2003	NA	27	C	No	
8	55	Clear cell	2C	6/05/2003	16/06/2003	3/11/2003	40	C	10/12/2003	Possible Recurrence
9	73	Mucinous (borderline)	4	4/06/2003	24/11/2003	5/01/2004	**170**	G	5/01/2004	Recurrence
10	52	Endometroid	1C/3C	18/06/2003	19/08/2003	5/01/2004	61	C/P	29/01/2004	NRD (?Psoas metastasis)
11	70	Serous (papillary)	4	8/07/2003	4/09/2003	19/01/2004	56	C	No	
12	33	Endometroid / Serous (borderline)	1C	27/08/2003	20/10/2003	17/11/2003	53	Cis/RT		
13					5/01/2004	23/02/2004		C/P	27/02/2003	NRD
14	68	Endometroid / Serous (papillary)	4B	9/09/2003	17/11/2003	Passed away	68	C		
15	75	Transitional cell	3C	30/09/2003	24/11/2003	16/02/2004	54	C/P	12/02/2004	NRD
16	39	Serous (non-ovarian)	no mets	6/10/2003	24/02/2004	Ongoing	**138**	C/P	Ongoing	
17	65	Mucinous (borderline) + pseudomyxoma	4	8/10/2003	19/01/2004	Ongoing	**101**	5FU/FA	Ongoing	
18	37	Clear cell	1C	15/10/2003	Not yet			C	Not yet	
19	42	Serous	4	19/11/2003	Not yet			C	Not yet	
20	73	Endometroid	1B	26/11/2003	16/02/2004	Ongoing	80	P	Ongoing	
21	63	Serous (papillary)	3C	9/12/2003	20/02/2004	Ongoing	71	C/P	Ongoing	

Cis = Cisplatin **C** = Carboplatin **P** = Paclitaxel
G = Gemcitabine **E** = Elopisode **NRD** = No residual disease

AVG = 63.72
MEDIAN = 53.5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