



Improving outcomes in ovarian cancer

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Ovarian cancer is the fourth most common cause of cancer mortality in New Zealand women. In 2001, there were 300 new cases of this disease and 175 deaths. While the incidence of ovarian cancer is slowly increasing, mortality is decreasing and the expected survival for women with this disease is lengthening.¹

Unfortunately, at diagnosis, the majority of women have advanced disease, and there is no screening test that has been shown to improve mortality. Improvements in treatment are therefore largely responsible for improved survival. Currently, despite advanced disease, many women survive several years beyond their initial diagnosis.

Surgical staging, the surgical debulking of intra-abdominal tumour, leaving minimal residual disease ('optimal debulking'), followed by intravenous (IV) platinum-based chemotherapy, is the cornerstone of the modern management of this disease.^{2,3}

Carboplatin, with or without paclitaxel, is the current accepted standard chemotherapy regimen. This optimal management is most easily achieved with a multidisciplinary team approach including gynaecological oncologists (gynaecological cancer surgeons) and medical oncologists.

In January 2006, Armstrong and her colleagues on behalf of the Gynecologic Oncology Group (GOG) in North America reported a large randomised trial.⁴ This showed an improvement in the survival of women with optimally de-bulked ovarian cancer when they were treated with chemotherapy which was in part delivered via an intraperitoneal (IP) catheter. Patients were given intravenous paclitaxel, followed by either IV cisplatin, or IP cisplatin plus IP paclitaxel. A 16-month survival advantage was reported for the IP arm.

Publication was accompanied by a Clinical Announcement from the National Cancer Institute (USA), which suggested...*strong consideration should be given to a regimen containing IP cisplatin (100 mg/m²) and a taxane whether given IV only, or IV plus IP.*⁵

Intraperitoneal therapy in ovarian cancer has been the subject of research for some years. As ovarian cancer is a disease that tends to spread to peritoneal surfaces rather than solid organs, it is hypothesised that the direct contact of intraperitoneal chemotherapy with the tumour nodules offers a more effective route of delivery of drugs than intravenous therapy, particularly in women with small volume residual disease.

Drugs also tend to have a longer half life in the peritoneum. The first positive randomised trial in intraperitoneal (IP) therapy for ovarian cancer was published in 1996, and there have been at least five other randomised trials published since. The practice, however, had not been adopted as standard treatment because of three reasons; firstly not all of the studies have been positive, secondly some of the studies

have been flawed methodologically, and lastly intra-peritoneal administration is associated with significant morbidity.

An independent (Cochrane) review has also recently been published, supporting the role of IP therapy in women with optimally debulked ovarian cancer.⁶ The meta-analysis reports a relative risk of recurrence and death of 0.79 in the patients who received IP therapy. This review, however, cautions that catheter related complications and toxicity need to be considered, and that more work needs to be done to determine optimal dose, timing, and mechanism of administration.

Publication of the most recent trial has led to IP chemotherapy being adopted widely in North America, however many centres have substantially modified the regimen because of toxicity. This toxicity is widely felt to be prohibitive, with 19% of patients developing neuropathy interfering with activities of daily living, and 46% developing grade 3 or 4 gastrointestinal complications (i.e. requiring hospitalisation).⁴

Evidence in favour of IP therapy, particularly from European Oncologists, has been criticised, and while the three largest trials have all been positive, each has also been flawed in some way.

The first trial used an obsolete control arm, and paradoxically found no significant survival advantage in those patients with the greatest expected benefit of IP therapy (those with minimal residual disease <0.5 cm).⁷ The second trial used a higher dose of platinum in the IP arm, and the benefit was of only marginal significance (one-tailed p value 0.05 for overall survival).⁸ The most recent trial also used higher platinum and paclitaxel doses in the IP arm, leaving open the possibility the benefit is dose rather than delivery-related. In this trial, only 42% of the IP patients received the planned 6 cycles of IP therapy, and 44% of patients in the IP arm went on to get non-protocol IV carboplatin and paclitaxel.⁴

Again, the control arm of cisplatin and paclitaxel used in this trial is no longer standard IV therapy. Therefore there is no study demonstrating an IP regimen which is superior to the current standard IV therapy, and the regimen which has produced the most encouraging results can not be delivered to the majority of patients because of toxicity.

Most New Zealand specialists regularly treating gynaecological cancers are members of the New Zealand Gynaecological Cancer Group (NZGCG) whose aim is to improve the care of women with gynaecological cancer throughout New Zealand. Having reviewed the evidence, the opinion of the NZGCG is that trial results of IP chemotherapy are encouraging, and require further study. However this is a new treatment approach with documented morbidity, without direct evidence of superiority over the current standard of care; IV carboplatin with or without IV paclitaxel. The technique should therefore be further investigated in a standard, monitored fashion. The ideal way to do this is to take part in a large, well-governed, multi-centre clinical trial.

In the immediate future, further improvements in the outcome of ovarian cancer in New Zealand depend on a multifaceted approach; ensuring patients throughout the country have access to optimal surgery and chemotherapy. The NZGCG is committed to facilitating this process, and welcomes technological advances such as IP therapy.

However the data supporting IP therapy is open to interpretation, and is therefore incomplete.

We believe that (by opening a trial of IP treatment) we can contribute to increasing the body of knowledge about this treatment modality. We are working actively with the Australia New Zealand Gynaecological Oncology Group (ANZGOG) to implement an appropriate clinical trial of intraperitoneal chemotherapy in New Zealand in the next few months.

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