

Bevacizumab and ovarian cancer: what we know and the questions that remain

Ovarian cancer

Ovarian cancer is the sixth most common cancer in women in the UK. More than 200,000 women are diagnosed with it each year globally.

Outcomes from ovarian cancer are often poor. More than 125,000 women die of ovarian cancer globally each year. The poor survival is a consequence of the disease being difficult to detect, leading to diagnosis happening when the disease is already advanced for many women.

For women with advanced ovarian cancer there has been little improvement in five-year survival since the introduction of paclitaxel 15 years ago. Most women with advanced disease are not cured. The standard treatment (surgery and platinum-based chemotherapy) has changed little in the last ten years and no new drugs have been introduced. New approaches to treat the disease are urgently needed, making the ongoing trials into ways of treating ovarian cancer of vital importance.

Bevacizumab

Bevacizumab (also known as Avastin) is an anti-angiogenesis drug (see box). It is a humanised monoclonal antibody that represses the development of

Angiogenesis is the development of new blood vessels. Tumours need new blood vessels if they are to grow, to provide them with nutrients and oxygen. If tumour angiogenesis can be stopped, it may prevent the tumour from growing, which may improve the survival of patients.

new blood vessels. It is licensed for the treatment of metastatic colorectal, lung, renal, breast and brain cancers.

Disease progression in ovarian cancer is in part driven by vascular endothelial growth factor. Because of this, and the effectiveness of bevacizumab in treating other cancers, research has been carried out to see if it could also be useful as part of the initial treatment for women with ovarian cancer.

What we know about the effectiveness of bevacizumab for ovarian cancer

Recently, two large randomised phase III trials have reported results on the effect of bevacizumab on progression free survival. Both of these were first line trials following initial debulking surgery. In the GOG218 trial after surgery patients with advanced ovarian cancer were randomised to standard chemotherapy (with carboplatin and paclitaxel) or standard chemotherapy + bevacizumab, or standard chemotherapy + bevacizumab + continuation bevacizumab after chemotherapy had been completed (a total of up to 22 cycles of bevacizumab). 1,873 women took part in this trial. Preliminary data from the GOG218 trial show that adding bevacizumab to standard chemotherapy, and subsequently continuing bevacizumab after the end of chemotherapy significantly improves progression-free survival compared to standard chemotherapy alone (14.1 months compared to 10.3 months).

The ICON7 trial involved 1,528 women. 30% of these women were at high-risk of progression. Those women at high risk

Key points

- Ovarian cancer is a common cancer in women, killing 125,000 each year
- Little progress has been made in improving survival of women with the disease in the last 15 years
- There is now evidence that bevacizumab can improve progression-free survival, when used alongside chemotherapy and continued afterwards, particularly for women at high risk of disease progression
- Key questions remain over whether the improvement in progression-free survival translates into improved overall survival; what dose should be used and for how long; and how cost effective it is

were similar to those who participated in GOG218. The remaining 70% had less-advanced cancer. The trial compared standard chemotherapy alone (carboplatin and paclitaxel) with standard chemotherapy + bevacizumab + continuation bevacizumab after chemotherapy had been completed (a total of up to 18 cycles of bevacizumab). Initial results found that bevacizumab did significantly improve progression-free survival compared to standard chemotherapy alone (19.8 months compared to 17.4 months). The effect of bevacizumab was particularly strong among women at high risk of progression, increasing median progression-free survival from 10.5 months to 16 months.



Photo courtesy of Roche, ©F. Hoffmann-La Roche Ltd. Group Communications

In these two trials the absolute increases in progression-free survival are not large. They are largest in GOG218 and the high-risk sub-group in ICON7, raising the possibility that those at greatest risk benefit most from bevacizumab.

A third randomised phase III clinical trial (the OCEANS trial) has been conducted in 484 women with recurrent platinum-sensitive ovarian cancer. This trial compared standard chemotherapy (in this case carboplatin and gemcitabine) to standard chemotherapy + bevacizumab + continuation bevacizumab until the time of further progression of disease. OCEANS found that progression-free survival increased from 8.4 months to 12.4 months with the addition of bevacizumab.

Overall survival

Currently there is limited information available on the impact of bevacizumab on overall survival, as the trials discussed above require longer follow-up information. In the ICON7 trial, analyses done after 378 women had died showed that there was a trend of improved survival for those women receiving bevacizumab. In these early data the difference was not statistically significant. But for the 30% of women at high risk of progression the improvement was greater, increasing average overall survival from 28.8 months to 36.6 months in these women. The difference for the high risk subgroup was statistically significant. More evidence will be available for overall survival on the ICON7 trial in 2013.

Quality of Life

In ICON7 the quality of life at 54 weeks was significantly better than at baseline for both arms of the trial. The improvement in quality of life was slightly smaller in patients receiving bevacizumab compared to those receiving chemotherapy alone. This was probably due to the fact that women in the bevacizumab arm continued to attend hospital every three weeks for intravenous treatment, after the chemotherapy had finished. The dimensions of quality of life that were worse for patients taking bevacizumab were role and emotional function, appetite, financial worries and chemotherapy side effects, although the differences were not large.

Toxicity

Overall, bevacizumab is tolerated well when used to treat ovarian cancer. Toxicities observed in the phase III trials were generally mild and manageable. The use of bevacizumab for other disease sites has been associated with various serious side effects, including fistulae. One of the phase II trials of bevacizumab in advanced and recurrent ovarian cancer found worryingly high levels of gastro-intestinal perforations (11-15%). However, in both GOG218 and ICON7 the rate of potentially fatal gastro-intestinal toxicities was lower than expected (1-3%). The incidence of gastro-intestinal perforation may be higher in pre-treated patients and patients with a history of bowel obstruction. Grade 2 or greater hypertension was seen in around a fifth of patients in GOG218 and ICON7. Proteinuria, haemorrhage and

arterial thrombotic events and wound-healing problems were also observed.

Remaining questions

Overall survival

The ultimate aims of treatment of ovarian cancer are to improve the length and / or quality of patient survival. Progression-free survival is only an intermediate indicator. A statistically significant difference in progression-free survival may not result in an overall survival benefit for the patient. Currently, we do not have enough evidence to be sure that bevacizumab improves survival. The final results of the ICON7 trial, due in 2013, will help to fill this gap.

Treatment strategy

The available evidence leaves questions remaining as to what dose of bevacizumab should be used, and how long should bevacizumab be continued for. GOG218 used 15mg/kg of bevacizumab, while ICON7 used 7.5mg/kg, suggesting that 7.5mg/kg may be sufficient. Evidence from the arm of GOG218 where bevacizumab was used during chemotherapy but not during the maintenance phase indicates that maintenance doses of bevacizumab after chemotherapy has finished are important. That, together with the timing of the maximal treatment effect observed in ICON7, raises the possibility that prolonged therapy with bevacizumab beyond 12 months (possibly until progression) may be beneficial.

Cost-effectiveness

Bevacizumab is an expensive drug. A course of treatment costs more than £20,000 per patient. Evidence on the cost-effectiveness, balancing cost with improvements in survival and quality of life, is needed to inform decisions for bodies such as NICE. Cost-effectiveness data from ICON7 should be available in 2013.

Who benefits most from bevacizumab?

ICON7 and GOG218 both show that, adding, bevacizumab to chemotherapy can improve progression-free survival. There is also evidence from OCEANS and phase

II trials that bevacizumab may have a role in treating recurrent ovarian cancer. The identification of sub-groups of women who may benefit most from bevacizumab may be key to its cost-effective use. At the moment the only group that we can identify who appear to benefit more than others are those at highest risk of progression.

It may be possible to identify biomarkers to help indicate which individuals would benefit most from bevacizumab. This could be very helpful in deciding who should be treated with it, and who might be at risk of serious side-effects from it. Research seeking to address these questions is about to start based on samples from the ICON7 trial.

References

Perren T J, A M Swart, J Pfisterer et al. 2011: Bevacizumab in Ovarian Cancer: ICON7 – a Phase III Gynecologic Cancer InterGroup Trial, *New England Journal of Medicine*, **365**:26

Burger R A, M F Brady, M A Bookman et al. 2010: Phase III trial of bevacizumab (BEV) in the primary treatment of advanced epithelial ovarian cancer (EOC), primary peritoneal cancer (PPC), or fallopian tube cancer (FTC): A Gynecologic Oncology Group study. *J Clin Oncol* 25:18s (suppl; abstr LBA1).

Leary A, M Gore, 2011: Incorporating bevacizumab into ovarian cancer treatment: practical considerations. *American Society of Clinical Oncology Educational Book Manuscript* <http://www.asco.org/ASCOv2/Home/Education%20&%20Training/Educational%20Book/PDF%20Files/2011/zds00111000198.PDF> (accessed 21st September 2011)

Eskander R N, L M Randall, 2011: Bevacizumab in the treatment of ovarian cancer. *Biologics: Targets and Therapy* 5 pp1-5.

Credits

This briefing document is an output from the ICON7 trial, which was carried out by the Gynecologic Cancer InterGroup. It was written by Annabelle South, Ann Marie Swart, Max Parmar and Tim Perren. The ICON7 trial is funded by Roche (F. Hoffmann-La Roche Ltd.).

ICON7
Bevacizumab in Ovarian Cancer

CONCLUSIONS

Bevacizumab has shown promising results for treating ovarian cancer. This is particularly welcome given the lack of progress over the last 15 years in improving treatment for the disease. Randomised controlled trials shows that it can significantly improve progression-free survival. The effect appears largest in women at high risk of their disease progressing. There is also evidence that it may significantly improve overall survival for women at high risk of disease progression. Important questions still remain about the use of bevacizumab in ovarian cancer. Perhaps most important is, does the improvement

in progression-free survival translate to improvements in overall survival for those not at high risk of progression? What dose should be used and how long should we use it for? Reliable biomarkers that can predict benefit from bevacizumab are needed, and it is hoped that the translational research linked to trials will provide guidance on this in the next few years. Given the high costs of the drug, and the many competing claims on health funding, the issue of cost-effectiveness needs to be addressed. This has to wait until mature survival information is available.

RECOMMENDATIONS

- The addition of bevacizumab to standard chemotherapy (and maintained for at least 12 months after chemotherapy has been completed) should be considered for women with advanced ovarian cancer at a high risk of progression at the time of diagnosis. It should also be considered at the time of first relapse for women who have had a period of at least 6 months free of progression after completing first line platinum based chemotherapy
- In first line therapy, the decision on whether bevacizumab should be used for non-high-risk patients with ovarian cancer should be delayed until there is further evidence on its impact on overall survival and cost-effectiveness
- Research is needed to answer questions on dose, length of treatment and biomarkers that can predict who will benefit most from bevacizumab.

