# Commentary on the clinical trial reported by: Tewari KS, Sill M, Long III HJ, *et al.* Incorporation of bevacizumab in the treatment of recurrent and metastatic cervical cancer: a phase III randomized trial of the Gynecologic Oncology Group. J Clin Oncol 2013;(suppl; abstr 3)

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One of the highlights of the recent ASCO meeting was the presentation of the results of GOG 240 by Tewari on behalf of his co-investigators in a plenary session (1). This was a positive trial which reported a significant increase in overall survival (OS) of women with metastatic/recurrent cervical cancer who were treated with bevacizumab in combination with chemotherapy. This is likely to change the standard of care of women with recurrent/metastatic cervical cancer in well-resourced regions of the world in particular and deserves review and detailed discussion.

Although cervical cancer is preventable and curable when detected early, it remains a major cause of cancer deaths in poorly resourced and less well developed countries, but is also an important cause of morbidity and deaths particularly in socially disadvantaged women in developed countries (2,3). Cervical cancer was responsible for 275,000 deaths in 2008 and 85% of these occurred in developing countries which approximates 41,000 deaths annually in the developed world (2,3). The current standard of care for women with locally advanced cervical cancer is concurrent cisplatin chemotherapy and pelvic radiotherapy with expected survival rates of 60-80% depending on the FIGO stage at presentation (4). Unfortunately, a significant number of women will relapse after cisplatin and radiation and there are also many women who have metastatic disease at first presentation. The outcomes for women with metastatic disease as well those with locally recurrent cervical cancer who are not candidates for exenterative surgery are poor (4). The median OS of these patients is in the order of 12 months and the progression free survival (PFS) of five months with platinum based combination chemotherapies (4,5). The largest contemporary trial of cisplatin based combinations by the GOG in patients with Stage 4B, recurrent or persistent cervical cancer included just over 500 patients (5). The patients were randomised to receive one of four regimens—cisplatin-paclitaxel; cisplatin-vinorelbine; cisplatin-gemcitabine or cisplatin-topotecan. Response rates were similar in all four arms. The trial was stopped early for futility. There was a non-significant trend in favour of cisplatin-paclitaxel (OS 12.9 months) compared to the other three arms (OS 10-10.3 months) (5). The authors concluded that the results were disappointing and that there was a need to investigate biologic agents such as bevacizumab in combination with chemotherapy. They went onto do a phase 2 study of bevacizumab alone in this population of patients which subsequently led to GOG 240 which is discussed in detail below (6).

There is good evidence that angiogenesis plays a central role in cervical carcinogenesis and progression and a strong rationale for including an antiangiogenic therapy such as bevacizumab in the treatment of cervical cancer (7,8). The rationale was discussed in some detail by Tewari who pointed out the compelling association between activation of viral E6 and E7 genes in patients with high risk HPV subtypes with consequent induction of hypoxia inducible factor 1 (HIF1alpha) which up-regulates VEGF and stimulates angiogenesis (7). There is also evidence to show that angiogenesis is induced by the PI3K/mTOR pathway

as well as by E7 and E7 directly (8). In a phase 2 study by the GOG in 46 patients with metastatic cervical cancer after prior chemotherapy and radiation, bevacizumab was reported to have activity with 24% surviving progression free for six months and 11% having a partial response (6).

GOG 240 recruited 452 patients with recurrent/persistent/metastatic cervical cancer to a randomised controlled trial investigating the role of bevacizumab (1). They used a 2×2 factorial design and patients were randomised to receive chemotherapy with or without bevacizumab 15 mg/kg every three weeks. The chemotherapy regimens included cisplatin 50 mg/m$^2$ plus paclitaxel 135-175 mg/m$^2$ or Topotecan 0.75 mg/m$^2$ D1-3 plus paclitaxel 175 mg/m$^2$. Cycles were repeated every 21 days until progression, unacceptable toxicity or complete response. The primary endpoints included; whether the addition of bevacizumab would increase OS; if the non-platinum doublet improved OS and the tolerability of the four regimens based on CTCAE v3 and v4. The secondary endpoints included PFS and overall response rate (ORR) by RECIST v1.0 in all four arms. There were also a number of exploratory endpoints including HRQOL as well as prognostic markers such as nicotine dependence and circulating tumour cells and expression of VEGF isoforms which will be presented at a later date.

The sample size calculation of 450 was based on their aim of increasing the median OS from 12 to 16 months. There was a pre-planned analysis at 173 deaths to determine futility/superiority. The study was activated in 2009 and reached target accrual in January 2012. The trial population included 225 patients treated with chemotherapy alone and 227 treated with chemotherapy plus bevacizumab. The arms were well balanced. The majority of patients had squamous cell cancer (70%) with 20% having adenocarcinomas. Most were Caucasian (80%) and the majority had recurrent (70%) or persistent disease (10%) after cisplatin and radiotherapy while the rest had metastatic disease at initial presentation. About 55% of patients had locally recurrent pelvic disease after chemo-radiation. Almost 60% of patients recruited were ECOG 0 and the remainder ECOG 1.

The pre-planned analysis after 174 deaths was presented by Tewari at the SGO in 2013 where he reported that the topotecan and paclitaxel arm of GOG 240 was not superior or inferior to the cisplatin paclitaxel arm (median OS 15 *vs.* 12.5 months) (9). In January 2013 the primary trial endpoint was reached and in March ASCO made a rare exception and released the abstract into the public domain well before the ASCO presentation, in view of the findings which had the potential to alter the standard of care.

Tewari reported that with a median follow up of 20.8 months the median survival was 17 months with bevacizumab and 13.3 months with chemotherapy alone (HR 0.71; 95% CI, 0.54-0.94; P=0.00035) (1). Bevacizumab also improved PFS over chemotherapy alone. The median PFS in the bevacizumab group was 8.2 months compared with 5.9 months in the chemotherapy alone group (HR 0.67; 95% CI, 0.54-0.82; P=0.0002). The ORR with bevacizumab was 48% *vs.* 36% (P=0.008). There were 28 complete responses in the bevacizumab group and 14 in the chemotherapy alone arm. The benefit of the addition of bevacizumab was reported for both chemotherapy arms—cisplatin-paclitaxel ± bevacizumab-median OS 14.3 *vs.* 17.5 months (P=0.03) and topotecan-paclitaxel ± bevacizumab-median OS 12.7 *vs.* 16.2 months (P=0.08).

The median number of cycles of chemotherapy delivered was 6 [0-30] in the chemotherapy alone arms and 7 [0-36] in the chemotherapy plus bevacizumab arms. The adverse effects were described in detail. There were four treatment related deaths in both arms. Patients in the bevacizumab group experienced more toxicities in keeping with what is expected with bevacizumab—these includes hypertension > grade 2 (25% *vs.* 2%); thromboembolism (8% *vs.* 1%); grade 3 gastrointestinal fistulae (3% *vs.* 0%); grade 3 gastro-intestinal perforation (2% *vs.* 0%) and grade 3 genitourinary fistulae (2% *vs.* 0%).

Tewari presented a Forest Plot which demonstrated that that there were greater benefits of bevacizumab seen in particular subsets which includes patients aged between 48 and 56 years old; patients with recurrent/persistent disease (but not in the 76 patients with metastatic disease at presentation) and also in patients with squamous histology, but not in patients with adenocarcinomas. In addition, they found that recurrent disease in the pelvis after prior radiation did not preclude benefit from bevacizumab. However, the numbers in all the subsets were relatively small and are difficult to interpret and should not influence clinical decisions.

The HRQOL endpoints were briefly discussed. Quality of life was assessed using the Functional Assessment of Cancer Therapy—Cervix Trial Outcome Index scale (FACT-Cx TOI scale) to assess physical and functional well-being specific to cervical cancer, where a between-group overall score difference of five or more would indicate a clinically significant detriment to quality of life. The FACT-Cx score difference between patients receiving chemotherapy alone and patients receiving chemotherapy

 

plus bevacizumab was 1.2 points suggesting that there was no significant deterioration in HRQOL in the bevacizumab arm despite the increase in bevacizumab related toxicities.

Tewari concluded that this was the first time that a targeted agent significantly improved OS in a gynaecological cancer and that the four month increase in median OS in recurrent cervical cancer is clinically significant.

## Discussion of the results

Dr Gottfried Konecny was the discussant and emphasised the strong rationale for targeting VEGF in cervical cancer and concluded that GOG 240 was a practice changing study. I agree with his comments and conclusions but would like to raise a number of unanswered questions. The cost effectiveness analysis has yet to be presented, but is critically important given the cost of bevacizumab. Given, that the burden of cervical cancer is greatest in poorly resourced regions of the world, it is very unlikely that the results of this study will change the standard of care in these regions where the limited health dollars should be directed to screening and early detection as this has the potential to cure a large number of women. However, it is likely that the bevacizumab combination will be more widely used in well-resourced developed countries. We don't know whether 15 mg/kg is the optimal dose or whether 7.5 mg/kg (or even less) would be equivalent. This is an important question given the cost of bevacizumab. It is also conceivable that continuing on maintenance bevacizumab following the cessation of chemotherapy in responding patients would be beneficial as has been demonstrated in ovarian cancer trials and this is also an important question to address in future studies. There are a number of oral tyrosine kinase inhibitors such as pazopanib which have also been shown to have single agent activity in recurrent cervical cancer and warrant further investigation (10).

There is still debate in the community regarding what is the optimal chemotherapy combination to use in the recurrent setting. This study used cisplatin and paclitaxel which does have more toxicity than carboplatin and paclitaxel and this is clearly important in the recurrent setting when one of the aims of treatment is palliation and symptom control with an attempt to minimise adverse events. The median number of cycles administered was seven in the bevacizumab arm with a wide range from 0-36. It is hard to imagine that 36 cycles of chemotherapy would not be associated with significant toxicity and this raises the important question regarding what is the optimal number of cycles of chemotherapy and underscores the importance of investigating the role of maintenance bevacizumab after a defined number of cycles of chemotherapy. The Japanese GOG reported the results of a relatively large phase 3 study in 253 patients with very similar inclusion criteria to GOG 240, although they did have more favourable prognostic factors with 70% ECOG 0, 64% of recurrences were outside the treatment field, only 48% had prior cisplatin and 16% had a platinum free interval of less than six months. Patients were randomised to cisplatin-paclitaxel (TP) or carboplatin AUC 5 and paclitaxel 175 mg/m$^2$ (TC) (11) every three weeks for a maximum six cycles. This was a non-inferiority trial and they reported that the median OS was very similar in both groups (18.3 *vs.* 17.5 months, HR 0.99) and that there was less toxicity with TC. The PFS was 6.9 months in TP and 6.2 months in TC which was not statistically different. The three year survival was also similar 18% *vs.* 21%. Interestingly, they found that TP was superior in patients who had not had prior cisplatin (23.2 *vs.* 13 months; HR 1.57; 95% CI, 1.06-2.32) while TC was superior in patients who had received prior cisplatin (19.0 *vs.* 16.3 months; HR 0.69; 95% CI, 0.47-1.02), but this was an unplanned subset analysis. It is likely that in community practice the carboplatin and paclitaxel combination will be more widely used than cisplatin and paclitaxel as there is a lot of experience in combining it with bevacizumab. It is also possible that weekly paclitaxel might be more active than three weekly dosing, but this has not been subjected to a randomised trial in cervical cancer, to the best of my knowledge and is also worthy of investigation as weekly paclitaxel has also been reported to be antiangiogenic and would be much cheaper than bevacizumab (12).

Although, Tewari did not find any significant difference in HRQOL in this study, I think it would be very valuable to do a post hoc analysis in the whole cohort to try and determine what cancer related symptoms were present and study entry and whether these improved significantly as a result of treatment as this would strengthen the case for the addition of bevacizumab. It would also be important to look at the correlation between patient reported toxicities and clinician reported toxicities, as there are often important differences noted between clinician and patient grading of adverse effects (13). It would also be worthwhile to interrogate the data base and go back to clinical charts to try and see if it would be possible to identify which patients were at risk of severe toxicities such as treatment related deaths and fistulae. Only grade 3 or greater gastrointestinal, genitourinary fistulae and gastrointestinal perforations were reported,

 

but arguably all fistulae/perforations carry morbidity and it would be useful to know how many patients had a fistula or perforation of all grades as this information should be provided to patients who are going to be offered bevacizumab in clinical practice. Finally it is also important to appreciate that the patients were carefully selected for study entry and that they only included patients with ECOG 0-1 and it is likely that if all comers are treated the results would not be as good and the toxicities even greater.

GOG 240 is an important and practice changing trial. This important study like all good clinical trials raises even more important questions that will need to be addressed in well-designed prospective randomised clinical trials in patients with high risk earlier stage locally advanced cervical cancer as well as in those with recurrent or metastatic disease. The GOG have led the way in cervical cancer trials and are to be congratulated for their ongoing efforts to reduce the morbidity and mortality of cervical cancer.

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