

Mini Review

Bevacizumab and its Role in Ovarian Cancer Therapy

Nageswara Rao Alla*¹ and Harika S. Polamarasetty²

¹Department of Chemistry, Temple University, Philadelphia, PA – 19122, USA

²Department of Biochemistry, Gitam University, Visakhapatnam, Andhra Pradesh, India

*Corresponding author: Dr. Nageswara Rao Alla, Department of Chemistry, Temple University, Philadelphia, PA – 19122, USA, Tel: 267 467 5439; E-mail: allanagesh@gmail.com

Received: 07-29-2014

Accepted: 08-30-2014

Published: 09-03-2014

Copyright: © 2014 Alla

Ovarian cancer (OC) ranks seventh in the world [1] and fifth in the United States [2] as the cause of cancer death. About 90% of the ovarian cancers are epithelial ovarian cancers (EOC). Unlike other gynecological cancers, the cause of EOC is unknown [3]. The lack of specific symptoms for EOC leads to a delay in diagnosis and results in women presenting with advanced stages of the disease. The five year survival rate of advanced stage III or IV disease is estimated to be 20% [4]. Currently surgery is the most effective treatment option for early stage I-IIA ovarian cancers with 90% 5 year survival rate [5]. For woman with advanced stage disease, the standard treatment includes surgical debulking followed by adjuvant platinum-taxane based chemotherapy [6, 7]. Nonetheless, the overall survival (OS) is poor [8] and drug resistance emerges within 5 years in patients with advanced stage (OC) [9]. Recurrent ovarian cancer is classified into two groups based on platinum based therapy 1.) platinum resistant - if the cancer relapses within 6 months or 2.) platinum sensitive - if the cancer relapses after more than 6 months after completing platinum based chemotherapy [10]. Targeted therapy might improve the outcomes of advanced stage ovarian cancer.

Angiogenesis plays an important role in the progression of OC and is perfect target for targeted therapy strategies [11,12]. Angiogenesis mediated by vascular endothelial growth factor (VEGF) is critical for the normal ovarian function [13]. The link between VEGF overexpression, enhanced angiogenesis and the development and progression of ovarian cancer has been well-established. This makes anti-angiogenic agents directed against VEGF attractive drug candidates. Bevacizumab is a recombinant, humanized, monoclonal antibody which binds to VEGF and neutralizes activation of its receptors [14]. Phase II trials of

bevacizumab has shown tumor regression and delayed disease progression in women with ovarian cancer [15 -17].

Until now 4 Phase III randomized clinical trials have been conducted to determine the efficacy of combining bevacizumab with standard chemotherapy. The first two trials GOG-0218 and ICON7 tested the efficacy of bevacizumab plus standard chemotherapy followed by bevacizumab maintenance therapy as front-line treatment [18,19]. The other two efficacy trials OCEANS and AURELIA tested the efficacy of bevacizumab plus standard chemotherapy followed by bevacizumab maintenance therapy in platinum sensitive recurrent ovarian cancer setting [20,21]. A statistically significant improvement in the progression free survival (PFS) and objective response rate (ORR) was observed in all the four studies. However, it is important to note that there is no significant improvement in the OS in all these studies. A recent meta-analysis of the four trials has confirmed these results [25]. Without significant improvement in the OS use of bevacizumab as frontline therapy or in recurrent ovarian cancer setting is not cost effective [22,23]. Notably, AURELIA showed improvement in patient-related outcomes (PROs) unlike the other 3 trials [24]. GO 0218 trial did not show improvement in PROs, ICON7 showed slight worsening in PROs and OCEANS trial did not include PROs as end point [18-20].

The use of molecular profiling to predict responders vs non-responders to bevacizumab therapy is of importance as it would help decide which patients should receive the drug. In a preliminary analysis by Dr. Dowdy et al from Mayo clinic molecular sequencing was used to predict and

identify patients who can benefit from bevacizumab treatment [26]. These researchers used gene expression arrays to analyze the tissue from the ICON7 trial to determine the gene expression patterns of the ovarian tumors and use this data to predict the response to bevacizumab treatment [26]. BRCA might also have a predictive value, as patients with BRCA mutations and recurrent ovarian cancer have shown single agent activity of olaparib [27]. Patients who are BRCA negative and have platinum sensitive recurrent OC also exhibited response to olaparib therapy [28]. The potential role of VEGF-A as a biomarker has also been examined in bevacizumab studies. The association between high VEGF expression and disease progression [29] and poor OS [30] in platinum resistant OC has been observed in two separate phase II trials. Further research is needed to detect predictive markers of response to bevacizumab. Identification of these biomarkers would allow selection of patients who would benefit from this drug and reduce toxicity.

Interpreting the results from the trials mentioned earlier is complicated as these studies are different. The end points were evaluated using GCIg CA125 and RECIST criteria in GOG-0218 trial and only RECIST criteria in the ICON7 trial. The ICON 7 is a randomized two arm study and GOG-0218 is a randomized 3 arm study. Another important difference is, unlike other trials AURELIA is an open labelled study with no placebo control. Nevertheless, some key take home points from these studies are 1.) The dosage range in these trials was 7.5 mg/kg – 15 mg/Kg and in high risk OC patients there was no difference in PFS between patients receiving 15 mg/Kg and 7.5 mg/Kg. Therefore it is likely that the 7.5 mg/Kg dose would give less toxicity and also be more cost effective. 2.) The data from OCEANS and AURELIA trials suggests that, scheduling the administration of bevacizumab until the disease progression is optimal and 3.) The data in these phase III trials does not give a compelling evidence for the use of bevacizumab as a front-line therapy but supports the use of bevacizumab plus chemotherapy in patients with platinum-resistant recurrent OC.

The GOG-0218, ICON7, OCEANS and AURELIA trials have generated a wealth of information and these studies will be road maps for future studies/clinical trials towards a cure for OC. Trials are underway to test optimal duration, dosage and efficacy of different chemotherapeutic agents by themselves and anti-angiogenic agents plus chemotherapeutic agents. Positive results with bevacizumab led to testing of other targeted anti-angiogenic agents directed against platelet derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR), epidermal growth factor receptor (EGFR) and insulin growth factor 1(IGF 1) which are showing promising results. Another area of intensive research is the discovery of biomarkers with predictive and prognostic value in response to the therapeutic agents. The predictive biomarkers will help select patient population who would respond to the treatment and make the targeted

therapy more cost effective which is otherwise expensive. Overall this is a promising period in ovarian cancer research as it ushers new hopes towards a cure for this notoriously challenging disease

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors declare no conflicts of interest in preparing this article.

References

1. Gaitskell K, Martinek I, Bryant A, Kehoe S, Nicum S, Morrison J. Angiogenesis inhibitors for the treatment of ovarian cancer (review). Cochrane Database. 2009.
2. Ovarian Cancer Overview - American Cancer Society.
3. Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, The impact of eliminating socioeconomic and racial disparities on premature cancer deaths. *CA Cancer J Clin.* 2011, 61(4): 212–236.
4. Colombo N, Peiretti M, Parma G, Lapresa M, Mancari R et al. ESMO Guidelines Working Group: Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2010, 21(Suppl. 5): v23–v30.
5. Hennessy BT, Coleman RL, Markman M. Ovarian cancer. *Lancet.* 2009, 374: 1371–1382.
6. McGuire W, Hoskins W, Brady M, Kucera P, Partridge E, Look K et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. *N Engl J Med.* 1996, 334: 1–6.
7. Piccart M, Bertelsen K, James K, Cassidy J, Mangioni C, Simonsen E et al. Randomized intergroup trial of cisplatin-paclitaxel versus cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer: three-year results. *J Natl Cancer Inst.* 2000, 92: 699–708.
8. Siegel R, Naishadham D and Jemal A. Cancer statistics for Hispanics/Latinos, 2012. *CA Cancer J Clin.* 2012, 62: 21-153.
9. Heintz A, Odicino F, Maisonneuve P, Quinn M, Benedet J et al. Carcinoma of the ovary. FIGO 26th annual report on the results of treatment in gynecological cancer. *Int J Gynaecol Obstet* 95. 2006, (Suppl. 1): S161–S192.

10. Markman M, Rothman R, Hakes T, Reichman B, Hoskins W et al. Second-line platinum therapy in patients with ovarian cancer previously treated with cisplatin. *J Clin Oncol.* 1991, 9: 389–393.
11. Sledge GW Jr, Miller KD. Angiogenesis and antiangiogenic therapy. *Curr Probl Cancer.* 2002, 26: 1-60.
12. Folkman J. What is the evidence that tumors are angiogenesis dependent? *J Natl Cancer Inst.* 1990, 82: 4-6.
13. Masoumi Moghaddam S, Amini A, Morris DL, Pourgholami MH. Significance of vascular endothelial growth factor in growth and peritoneal dissemination of ovarian cancer. *Cancer Metastasis Rev.* 2012, 31:143–162.
14. Monk BJ, Han E, Josephs-Cowan CA, Pugmire G, Burger RA. Salvage bevacizumab (rhuMAB VEGF)-based therapy after multiple prior cytotoxic regimens in advanced refractory epithelial ovarian cancer. *Gynecol Oncol.* 2006, 102: 140-144.
15. Burger RA, Sill MW, Monk BJ, Greer BE, Sorosky JI. Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: a Gynecologic Oncology Group study. *J Clin Oncol.* 2007, 25: 5165-5171.
16. Cannistra SA, Matulonis UA, Penson RT. Phase II study of bevacizumab in patients with platinum-resistant ovarian cancer or peritoneal serous cancer. *J Clin Oncol.* 2007, 25: 5180-5186.
17. Garcia AA, Hirte H, Fleming G. Phase II clinical trial of bevacizumab and low-dose metronomic oral cyclophosphamide in recurrent ovarian cancer: a trial of the California, Chicago, and Princess Margaret Hospital Phase II Consortia. *J Clin Oncol.* 2008, 26: 76-82.
18. Burger RA, Brady MF, Bookman MA. Incorporation of bevacizumab in the primary treatment of ovarian cancer. *N Engl J Med.* 2011, 365:2473-2483.
19. Perren TJ, Swart AM, Pfisterer J. A phase 3 trial of bevacizumab in ovarian cancer. *N Engl J Med.* 2011. 365: 2484-2496.
20. Aghajanian C, Blank SV, Goff BA. OCEANS: A randomized, doubleblind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. *J Clin Oncol.* 2010, 30: 2039-2045.
21. Pujade-Lauraine E, Hilpert F, Weber B. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. *J Clin Oncol.* 2014, 32: 1302-1308.
22. Cohn D, Kim K, Resnick K, O'Malley D, Straughn J Jr. At what cost does a potential survival advantage of bevacizumab make sense for the primary treatment of ovarian cancer? A cost-effectiveness analysis. *J Clin Oncol.* 2011, 29: 1247–1251.
23. Lesnock J, Farris C, Krivak T, Smith K, Markman M. Consolidation paclitaxel is more cost-effective than bevacizumab following upfront treatment of advanced epithelial ovarian cancer. *Gynecol Oncol.* 2011, 122: 473–478.
24. Stockler MR, Hilpert F, Friedlander M. Patient-reported outcome results from the open-label phase III AURELIA trial evaluating bevacizumab containing therapy for platinum-resistant ovarian cancer. *J Clin Oncol.* 2014, 32: 1309-1316.
25. Zhou M, Yu P, Qu X, Liu Y, Zhang J. Phase III Trials of Standard Chemotherapy with or without Bevacizumab for Ovarian Cancer: A Meta- Analysis. *PLoS ONE.* 2013, 8(12): e81858.
26. Mayo Clinic. "Ovarian cancer subtypes may predict response to bevacizumab." *Science Daily.* 1 June 2014.
27. Fong PC, Boss DS, Yap TA. Inhibition of poly (ADP-ribose) polymerase in tumors from BRCA mutation carriers. *N Engl J Med.* 2009, 361: 123–134.
28. Gelmon KA, Tischkowitz M, Mackay H. Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study. *Lancet Oncol.* 2011, 12: 852–861.
29. Chambers SK, Clouser MC, Baker AF, Roe DJ, Cui H et al. Overexpression of tumor vascular endothelial growth factor A may portend an increased likelihood of progression in a phaseII trial of bevacizumab and erlotinib in resistant ovarian cancer. *Clin Cancer Res.* 2010, 16: 5320–5328.
30. Madsen CV, Steffensen KD, Olsen DA, Waldstrøm M, Smerdel M et al. Serial measurements of serum PDGF-AA, PDGF-BB, FGF2, and VEGF in multiresistant ovarian cancer patients treated with bevacizumab. *J Ovarian Res.* 2011, 5: 23.