International Journal for Pharmaceutical Research Scholars (IJPRS)

V-4, I-3, 2015 ISSN No: 2277 - 7873

REVIEW ARTICLE

A Review - Novel Treatment Approach in Ovarian Carcinoma

Talath Fatima*, Nazima Sultana, Syeda Karishma, Afiya Ansari, Osman Ahmed

Deccan School of Pharmacy, Hyderabad-01, Telangana, India.

Manuscript No: IJPRS/V4/I3/00175, Received On: 18/09/2015, Accepted On: 26/09/2015

ABSTRACT

Ovarian cancer is considered to be the fourth most common and life threatening type of cancer in females. Contemporary studies have shown that, ovarian cancer is not a single disease, but, a range of associated cancers having distinctive genetic attribute that may show an impact on response to the therapy. This malignancy and increased rate of deaths in women is due to the complication in prompt identification of the disease. For the management of ovarian cancer, it includes Cytoreductive surgery and also Platinum-based chemotherapy. Various therapies such as antibody therapy, adoptive cell therapy, vaccine strategies, and combinatorial immunotherapy have been proven effective at certain level. Beta blockers are the medications which are used to reduce the mortality and morbidity in heart diseases. There are 100 beta blockers known, but for the clinical use only 30 are known to be convenient. A recent study highlights that the use of non selective beta blockers by the patients with ovarian carcinoma may survive longer than the patients taking other beta blockers or none. It was found that, the women who took any of the beta blockers; the average overall survival has been noted as 47.8 months in contrast to the women who are non-users of beta blockers showing the survival rate of about 42 months. The women who took non-selective beta blockers survived longer when compared to the women who took selective agents of beta -1 adrenergic receptor. The main aspect of the review is to provide awareness for the prolonged survival of the patients with carcinoma of the ovary by the use of specific type of beta blockers.

KEYWORDS

Ovarian Cancer, Cytoreductive Surgery, Combinatorial Immunotherapy, Non Selective Beta Blockers, Beta -1 Adrenergic Receptor

INTRODUCTION

As per the estimation of American cancer society, in 2013, around 15,500 women died of ovarian cancer in United States. Contemporary studies have shown that, ovarian cancer is not a single disease, but, a range of associated cancers having distinctive genetic attribute that may show an impact on response to the therapy[1]. This is considered to be the fourth most common and life threatening type of cancer in females and is the major cause of death among all the gynecological malignancies all over the world[2]. This malignancy and increased rate of deaths in women is due to the complication in prompt identification of the disease. When it is confined to the ovary, this type of carcinomas causes very few indications which may become difficult to detect at a very early stage. And, as the ovarian cancer is asymptomatic at prior stages, these spreads to other parts, other than ovaries, such as pelvis and abdomen and also leads to the malignancy in those parts which may be lethal during the lifetime[3]. In the advance stages the symptoms that may be observed are swelling or

***Address for Correspondence:**
Ms. Talath Fatima
Deccan School of Pharmacy, Hyderabad,
Telangana State, India.
E-Mail Id: talath1012@gmail.com

bloating of abdomen, loss of weight, pain in the region of pelvis, constipation, polyuria etc.[4,5]. Almost all cases reach to third and fourth stages i.e., the advanced stages during the presentation, in ovarian cancer[6]. Mainly, for the management of ovarian cancer, it includes cytoreductive surgery and also platinum-based chemotherapy.[7] Various therapies such as antibody therapy, adoptive cell therapy, vaccine strategies, and combinatorial immunotherapy have been proven effective at certain level. New therapeutic strategies which help in the better outcomes for the survival of the patients with ovarian cancer are getting more advanced.[8]

Common Therapeutic Approaches

Antibody Therapy

Since last two decades the antibody – based therapies became well established strategies for treating solid tumors and other hematologic carcinomas. Many antibodies have been used for treating the ovarian carcinoma. Some of which are Bevacizumab, which is the humanized monoclonal antibody, which gets attached to VEGF (vascular endothelial growth factor) receptor ligand.[9] Other antibody Catumaxomab, which is bispecific, trifunctional antibody governed inimical to Epithelial Cell Adhesion Molecule (EpCAM) and the T cell antigen CD3.[10] Cetuximab and Panitumumab are also significant in the treatment of ovarian cancers but at certain levels. TAM-targeting antibodies also contribute in the generation of potent antitumor responses.[8]

Immune Checkpoint Inhibitors

It provides immunotherapeutic approach to the carcinoma treatment. Few immune checkpoint inhibitors such as CTLA-4 (Cytotoxic T Lymphocyte-associated protein-4) or CD152 plays a prominent role in regulation of T-cell activation. This may help in the tumor clearance.[11] Other immune checkpoints such as PD-1 (programmed cell death protein-1) and its ligand PD-L1 can be targeted to immunosuppression that is reverse-tumor mediated.[12] In addition to this, the use of IDO (Indoleamine 2, 3 dioxygenase) which is the leading metabolic immune regulator also helps in the therapy of ovarian carcinoma.[13]

Vaccine Strategies

This involves the eradication of the tumor cells with the help of vaccines. They may include-

- *Ex vivo* DC Vaccines.
- *In vivo* DC Vaccines.
- Whole tumor DC-based vaccines.
- Recombinant viral vaccines.
- Peptide vaccines.

Adoptive Cell Therapy

This is an immunotherapeutic approach, for the induction of cancer regression utilizes autologous or allogenic antitumor lymphocytes.

Combinatorial Therapy

For the maximum antitumor immune response combinatorial therapy may be beneficial. By the combination of various immunotherapies various phases of tumor decamp can be targeted, initiating the probability additive and synergistic outcomes between the agents.

These immune therapies hold a greater potential in the treatment of ovarian cancers but at a required level[8]. The high degree of survival can be achieved by the use of various drugs as mentioned below.

Novel Treatment Strategies for Ovarian Carcinoma

Beta Blockers

Beta blockers which are also known as beta adrenergic blocking agents or beta antagonists are the medications which are used to reduce the mortality and morbidity in heart diseases.[14] There are mainly three types of known beta receptors. They are β_1, β_2 and β_3 receptors. The location of these receptors varies accordingly.[15]

β_1 adrenergic receptors- heart and kidneys.

β_2 adrenergic receptors- lungs, liver, gastrointestinal tract, uterus, skeletal muscles etc.[16]

β_3 adrenergic receptors- adipose cells or fat cells.[17]

Clinical Pharmacology

While furthermore, there are 100 beta blockers known, but for the clinical use only 30 are known to be convenient.[18] The beta blockers that are soluble in water are likely to have prolonged half life when compared to the beta blockers soluble in lipids, which usually has shorter half lives. The water soluble beta blockers are eliminated through the body by means of kidney whereas the lipid soluble beta blockers are metabolized into the liver.[19]

Table 1: Generations of beta blockers[20]

Generation	Properties	Drugs
1.	Non-selective No Vasodilation	Propanolol, Timolol, Pindolol, Nadolol,Sotalol.
2.	Beta1-Selective without vasodilation. Beta1-Selective with vasodilation.	Atenolol, Bisoprolol, Metoprolol. Nebivolol, Acebutolol.
3.	Non selective with vasodilation	Carvedilol, Bucindolol.

After administrating orally many of these drugs are easily absorbed. There is a considerable elevation in the plasma half life when the biological half-life of beta blockers is increased. Generally, when more is the dose the biological effect is also more. Prolonged acting preparations are meant for severe conditions such as hypertension, angina etc.[21]. Many beta blockers are considered to be pure antagonists when clinically used. But hardly, few of them are considered to be partial agonists. Depending upon the disease, the relative density of beta-1 and beta-2 receptors varies. Usually, in myocardial infarction, there is a down regulation of beta-1 receptors.[22,23]

Mechanism of Action

The effects of epinephrine, nor epinephrine and dopamine (catecholamine) on the diseases of heart are confronted by beta blockers that occupy the beta receptors. The cardiac sarcolema contains beta-1 receptors and this is in association with the system of G-protein coupled adenyl cyclase. The activated receptor is integrated with adenyl cyclase and the origination of Cyclic Adenosine Monophosphate (CAMP) takes place when the catecholamines trigger the receptors. The elevated calcium is introduced into the cytosol by the phosphorylation of membrane calcium channel by Protein Kinase A (PKA) which is activated by the second messenger CAMP. This Protein kinase A also elevates the release of calcium from sarcoplasmic reticulum. This calcium leads to the positive ionotropic effect. Other effect is the lusitropic effect which shows the phosphorylation of troponin 1 and phospholamban by PKA. The positive dromotropic effect is the speed conduction of AV node and conduction tissue.[21]

Manifestations for the Use of Beta Blockers[20]

Strongly Indicated (Level-1) Other Indications (Level-2)	Post myocardial infarction Heart failure (systolic) • Hypertension • Cardiomyopathy (hypertrophic) • Marfan's Syndrome • Neurocardiogenic syncope • Mitral stenosis • Chronic stable angina

Contraindications

- Acute bronchospasm.
- Bradycardia.

- Atrioventricular (AV) block at high grade.
- Depression
- Cardiogenic shock
- Peripheral Arterial Disease (Symptomatic)[21]

The use of beta blockers is considered to be very useful in many diseases especially heart diseases. It has persistently shown the reduction in the mortality rate upto 30%. Hospitalizations have been reduced to 48% and around 38% reduction in sudden deaths mainly due to chronic heart diseases.[24,25]

Prolongation in Survival of Patients with Ovarian Cancer Using Beta Blockers

A recent study highlights that the use of non selective beta blockers by the patients with ovarian carcinoma may survive longer than the patients taking other beta blockers or none.[26] In preclinical studies, perpetuate adrenergic activation foster the proliferation of ovarian carcinoma. Hence, the influence of beta adrenergic blockade on women with carcinoma of the ovary was analyzed through the clinical outcomes by the researchers. The medical data of women who are treated for ovarian cancer also taking beta blockers directed for other reasons such as hypertension, Post myocardial infarction, and cardiac arrhythmias, along with chemotherapy is taken. Researchers found that, the women who took any of the beta blockers, the average overall survival has been noted as 47.8 months in contrast to the women who are non-users of beta blockers showing the survival rate of about 42 months. When the type of beta blocker taken was examined, there were prominent variations. The women who took non-selective beta blockers survived longer (94.9 months) when compared to the women who took selective agents of beta -1 adrenergic receptor who lived for about 38.0 months only. Hypertension was corresponding to the decline in comprehensive survival, but by the use of these non-selective beta blockers, the patients survived longer even with hypertension. The survival rate was noted to be 90.0 months in contrast to non-users of beta blockers who survived approximately 34.2 months. This broad retroactive is the first one which evidently shows the blocking characteristics of stress retaliation can see progress in the survival of the patients with ovarian cancers. Furthermore studies are being carried out to examine the mechanism involved in the survival of patients with ovarian cancers using beta blockers.[27]

CONCLUSION

Ovarian cancer is still the fourth cause of death by cancer among women and the most fatal among gynecological tumors. Attempts have been made to study several treatments for the patients with ovarian carcinoma, predominantly who still present with advanced stages. Though there are upcoming numerous treatments, the survival rate of patients presenting carcinomas of the ovary is declining probably. The prolongation of survival in the ovarian cancer patients can be improved by the use of non selective beta blockers, according to the recent study. This serves as a cornerstone for perceptive analysis or exploration into repurposing cardiovascular medications to the therapeutics of carcinomas. Although considerable efforts have been already made to study the use of beta blockers, extensive clinical trials on the impact of these drugs which may open up new treatment options for ovarian cancers are essential to prolong the rate of survival of patients in the foreseeable future.

ACKNOWLEDGEMENT

Most importantly we are thankful to the Almighty, who is the creator and director of all that initial and final modes to destiny. We take this opportunity to express our deep sense of gratitude, respect to Prof. Dr. Osman Ahmed, Vice-Principal, Deccan School of Pharmacy, Hyderabad, for encouraging us during this work.

ABBREVATIONS

VEGF- Vascular Endothelial Growth Factor.

EpCAM- Epithelial Cell Adhesion Molecule.

TAM- Tumor Associated Macrophages.

CTLA-4- Cytotoxic T Lymphocyte-associated protein-4.

PD-1- Programmed Cell Death Protein-1.

IDO- Indoleamine 2, 3 dioxygenase.

DC Vaccines- Dendritic Cell Vaccines.

CAMP- Cyclic Adenosine Monophosphate

PKA- Protein Kinase A.

REFERENCES

1. Tabassum, N., Raheem, Z., & SA, A. (2013). A Review: Progress against the Treatment of Ovarian Cancers. *Advanced Journal of Phytomedicine and Clinical Therapeutics*, *1*(5), 528-536.
2. Jayson, G. C., Kohn, E. C., Kitchener, H. C., & Ledermann, J. A. (2014). Ovarian cancer. *The Lancet*, *384*(9951), 1376-1388.
3. Goff, B. A., Mandel, L., Muntz, H. G., & Melancon, C. H. (2000). Ovarian carcinoma diagnosis. *Cancer*, *89*(10), 2068-2075.
4. Smith, L. H., Morris, C. R., Yasmeen, S., Parikh-Patel, A., Cress, R. D., & Romano, P. S. (2005). Ovarian cancer: can we make the clinical diagnosis earlier?. *Cancer*, *104*(7), 1398-1407.
5. Karst, A. M., & Drapkin, R. (2009). Ovarian cancer pathogenesis: a model in evolution. *Journal of Oncology*, *2010*.
6. Herzog, T. J. (2006). The current treatment of recurrent ovarian cancer. *Current Oncology Reports*, *8*(6), 448-454.
7. Baldwin, L. A., Huang, B., Miller, R. W., Tucker, T., Goodrich, S. T., Podzielinski, I., & Seamon, L. G. (2012). Ten-year relative survival for epithelial ovarian cancer. *Obstetrics & Gynecology*, *120*(3), 612-618.
8. Chester, C., Dorigo, O., Berek, J. S., & Kohrt, H. (2008). Immunotherapeutic approaches to ovarian cancer treatment. *Clinical Cancer Research*, *6*, 9.
9. Ferrara, N., Gerber, H. P., & LeCouter, J. (2003). The biology of VEGF and its receptors. *Nature Medicine*, *9*(6), 669-676.
10. Bellone, S., Siegel, E. R., Cocco, E., Cargnelutti, M., Silasi, D. A., Azodi, M., & Santin, A. D. (2009). Overexpression of epithelial cell adhesion molecule in primary, metastatic, and recurrent/chemotherapy-resistant epithelial ovarian cancer: implications for epithelial cell adhesion molecule-specific immunotherapy. *International Journal of Gynecological Cancer*, *19*(5), 860-866.
11. Korman, A. J., Peggs, K. S., & Allison, J. P. (2006). Checkpoint blockade in cancer immunotherapy. *Advances in Immunology*, *90*, 297-339.
12. Terme, M., Ullrich, E., Aymeric, L., Meinhardt, K., Desbois, M., Delahaye, N., & Zitvogel, L. (2011). IL-18 Induces PD-1–Dependent Immunosuppression in Cancer. *Cancer Research*, *71*(16), 5393-5399.
13. Takikawa, O. (2005). Biochemical and medical aspects of the indoleamine 2, 3-dioxygenase-initiated L-tryptophan metabolism. *Biochemical and Biophysical Research Communications*, *338*(1), 12-19.
14. Mukherjee, D., Fang, J., Chetcuti, S., Moscucci, M., Kline-Rogers, E., & Eagle, K. A. (2004). Impact of combination evidence-based medical therapy on mortality in patients with acute coronary syndromes. *Circulation*, *109*(6), 745-749.
15. Frishman, W. H., Cheng-Lai, A., & Nawarskas, J. (2005). *Current cardio-vascular drugs*. Springer Science & Business Media.
16. Arcangelo, V. P., & Peterson, A. M. (Eds.). (2006). *Pharmacotherapeutics for advanced practice: a practical approach* (Vol. 536). Lippincott Williams & Wilkins.
17. Clément, K., Vaisse, C., Manning, B. S. J., Basdevant, A., Guy-Grand, B., Ruiz, J., & Strosberg, A. D. (1995). Genetic variation in the β3-adrenergic receptor and an increased capacity to gain weight in patients with morbid obesity. *New England Journal of Medicine*, *333*(6), 352-354.
18. Frishman, W. H., & Charlap, S. (2003). Alpha-and beta-adrenergic blocking drugs. *Cardiovascular Pharmacothera-peutics. New York, NY: McGraw-Hill*, 67-97.

19. Koch-Weser, J., & Frishman, W. H. (1981). beta-Adrenoceptor antagonists: new drugs and new indications. *The New England Journal of Medicine*, *305*(9), 500.

20. Opie, L. H., & Gersh, B. J. (2012). *Drugs for the Heart*. Elsevier Health Sciences., 7th edn. Philadelphia: Elsevier, 2008.

21. Mansoor, A. H., & Kaul, U. (2009). Beta-blockers in cardiovascular medicine. *Journal of Association of Physicians of India*, *57*, 7-12.

22. Helfand, M., Peterson, K., & Christensen, V. (2007). Drug class review on beta adrenergic blockers. *Final Report Update*, *4*.

23. Benovic, J. L., Bouvier, M., Caron, M. G., & Lefkowitz, R. J. (1988). Regulation of adenylyl cyclase-coupled beta-adrenergic receptors. *Annual Review of Cell Biology*, *4*(1), 405-428.

24. Foody, J. M., Farrell, M. H., & Krumholz, H. M. (2002). β-blocker therapy in heart failure: scientific review. *JAMA*, *287*(7), 883-889.

25. Teerlink, J. R., & Massie, B. M. (2000). The role of beta-blockers in preventing sudden death in heart failure. *Journal of Cardiac Failure*, *6*(2 Suppl 1), 25-33.

26. Watkins, J. L., Thaker, P. H., Nick, A. M., Ramondetta, L. M., Kumar, S., Urbauer, D. L., & Sood, A. K. (2015). Clinical impact of selective and nonselective beta-blockers on survival in patients with ovarian cancer. *Cancer*, *121*(19), 3444-3451.

27. Bunch, K. P., & Annunziata, C. M. (2015). Are beta-blockers on the therapeutic horizon for ovarian cancer treatment?. *Cancer*, *121*(19), 3380-3383.

