



Current Concepts in Role of Bilateral Salpingo-Oophorectomy in Non-Hereditary Metastatic Carcinoma of Breast: Review Article

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Abstract

Management of Carcinoma breast with metastatic disease in premenopausal woman is expanding from tamoxifen only to additional ovarian suppression with Gonadotropin Releasing Hormone agonists (GnRh), Aromatase inhibitors and or bilateral oophorectomy. Direct comparison or therapeutic superiority of medical vs. surgical ovarian suppression is reported in very few studies. This review focuses on consensus of recent articles on the benefits and risks of medical versus surgical ovarian suppression in perimenopausal women with non-hereditary and hormone receptor positive metastatic breast cancer. Surgical ovarian ablation seems to be cost-effective to medical therapy as adjuvant therapies in metastatic breast cancer with add on benefit of preventing ovarian cancer. However counseling regarding side-effects, risk-benefit ratio and quality-of-life after surgical menopause need to be addressed.

Introduction

The incidence of carcinoma breast is rising in both developed as well as developing countries. In India, in year 2012, 144,937 women are diagnosed with breast cancer and 70,218 died of it [1]. Breast cancer can be broadly divided into three different types- hormone-receptor (HR+ve) breast cancer (ER [Estrogen receptor]-positive or PR [Progesterone receptor]-positive), the human epidermal growth factor receptor (HER2+ve) tumors and triple-negative disease. Each one of these express different clinical course and require distinct treatment strategies. HR+ve disease have fair prognosis with longer cancer free period and tend to relapse in musculoskeletal system. Triple-negative breast cancer and HR-ve (hormone-receptor negative), HER2+ve breast cancer are aggressive types with a propensity to metastasize to brain and other viscera.

Women with metastatic disease require systemic drug therapy and include hormonal, anticancer agents or targeted drugs. Surgery with or without radiotherapy may be useful in selective cases. Women with HR+ve cancers are treated with hormonal therapy with or without Tamoxifen. This may be combined with any of the targeted drugs like palbociclib, everolimus etc. Chemotherapy is the main modality treatment for triple negative cancers. Trastuzumab, Pertuzumab are useful in HER2-positive tumors. HER2-negative tumors are chemosensitive and hormonal agents can be used if they are positive for HRs. Targeted drugs like PARP inhibitor are under trials. National Comprehensive Cancer Network advises to consider patient age, patient desire for treatment and give thorough counseling regarding expected survival gain with each therapeutic modality before initiating treatment [2].

Conservative breast surgery or Mastectomy is done in early stages but in advanced cases, treatment is challenging even with the available time tested therapies. Role of Risk Reducing Bilateral Salpingo-Oophorectomy (RRSO) in hereditary breast ovarian cancer syndromes is proven, but in non-hereditary breast cancer with distant metastases, Bilateral Salpingo-Oophorectomy (BSO) is debatable with no conclusive data till date.

Additional ovarian ablation either medical (GnRH agonists, Aromatase inhibitors) or surgical (BSO) is to be offered to premenopausal women. GnRH agonists, combination of tamoxifen with GnRH agonists, Aromatase inhibitors have replaced surgical castration in few studies with their comparable therapeutic efficacy to BSO to attain a 'total estrogen blockade' [3]. With the recently published data pertaining to disease free survival, overall survival rates, cost-effectiveness, recurrence rates, risk benefit ratio of hormonal and chemotherapy with and without BSO in advanced carcinoma

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Table 1: Studies comparing various available treatment modalities and their outcomes in metastatic breast cancer.

Authors Year, (Ref.)	Hormone Receptors (HR) Status	Type of Study (No. of Patients)	Treatment received (OA/T/G/GnRH/Exemestane/Aromatase inhibitor)	Outcome
Ingle et al. [25]	Unknown	RCT (53)	Ovarian Ablation surgery (OA-S) versus Tamoxifen(T)	No difference in outcomes
Buchanan et al. [26]	Any HR status	RCT (122)	OA(S) versus T	No difference in outcomes
Boccardo et al. [3]	HR-ve, Unknown HR status	RCT (48)	OA(S/XRT)versus OA+T versus Goserelin (G) versus G+T	No difference in outcomes
Sawka et al. [27]	HR+, Any HR status	RCT (39)	OA(S/ Irradiation-XRT)versus T	No difference in outcomes
Crump et al. [28]	HR+, or unknown HR	Meta-analysis (228)	T versus OA	No difference
Taylor et al. [21]	Any HR	RCT (136)	BSO (n = 67) or G (n = 69).	No difference
Love et al. [29]	Any HR status	RCT (709)	BSO+T versus observation	5-year disease-free survival rate of treatment arm was 75% and 58% for observation arm .The overall survival rate was 78% for treatment arm and 70% for observation arm. Only women who had ER+ve tumors benefited.
SOFT Trial 2015, [22]	HR+ , HER-2-Negative	RCT (3066)	5 years of T, T plus OA or exemestane plus OA.	Adding OA to T did not provide a significant benefit in the overall study population. In premenopausal, the addition of OA improved disease outcomes.
Suh KJ et al. [19]	HR-+ve, HER2 negative either recurrent or metastatic disease	Retrospective Study (66)	Aromatase inhibitors with GnRH agonists in 64% and BSO in 36%.	Clinical benefit was higher (88%) in BSO group as compared with GnRH agonist (69%) group with a longer Progression free survival in BSO group.
TEXT Trial 2018, [23]	HR+, HER-2-Negative	RCT (2672)	5 years of T, T plus OA or exemestane plus OA.	Higher rates of both disease-free and overall survival than T alone. The use of exemestane plus OA resulted in even higher rates of freedom from recurrence.

OA: Ovarian Ablation; OA-S: Ovarian Ablation Surgery; T: Tamoxifen; OA XRT: Ovarian Ablation radiation; G: Goserelin (GnRh agonist); BSO: Bilateral Salpingo Oophorectomy; SOFT: Suppression of Ovarian Function Trial; TEXT: Tamoxifen and Exemestane Trial; RCT: Randomised Controlled Trial

breast patients, performing BSO is on the rise. This article reviewed recent literature on the same.

Methodology

This article was written after extensive search for electronic medical database in English by using keywords like metastatic carcinoma breast, hormonal therapy, laparoscopic salpingo-oophorectomy, endocrine therapy in breast cancer. Bibliographies of the pertinent articles were analyzed, reviewed and then cross search for further similar studies was made. Inference and concise results regarding various therapeutic options and their risk benefit ratios including economic burden, adjuvant therapies and recurrence rates were included.

Results

The ratio of premenopausal to postmenopausal women is 1:4 among newly detected cases, of whom 60% test positive for HR and are candidates for hormonal therapy [4,5]. EBCTCG meta-analysis [6] is a review of 12 RCTs involving more than 2000 patients less than 50 years old and underwent oophorectomy or received ovarian irradiation. The risk of recurrence and mortality at 15 years follow-up was reduced by 25% in these women when compared with those who did not receive adjuvant therapy. This risk reduction was comparable to the results of chemotherapy.

Randomized controlled trial by Lee et al. [7], comparing surgical ovarian ablation (n=97 patients) with ovarian irradiation (n=61 patients) for metastatic breast cancer is of a conclusion that the choice between oophorectomy and radiation ablation is to be individualized

and focused on clinical variables more than the statistics related to efficiency of one over other treatment modalities [7].

The Cancer Care Ontario and American Society for Clinical Oncology mentioned that ovarian suppression is a better option in a premenopausal lady with HR+ve breast cancer either not tolerating or refusing chemotherapy. However this society does not recommend addition of ovarian ablation to chemotherapy and tamoxifen as there is no evidence demonstrating superiority [8]. ACOG opinion on elective and RRSO in 2008 suggested "ER+ve" positive metastatic breast cancer is treated first with aggressive hormonal therapy by suppressing the ovaries either medically or surgically. Premenopausal women taking aromatase inhibitors need concurrent suppression of ovarian function, and salpingo-oophorectomy may be a cost-effective alternative to long-term ovarian suppression using GnRH agonists [9]. National Institute for Health and Clinical Excellence, 2009 recommends tamoxifen with ovarian ablation as preferred therapy in HR+ve metastatic breast cancer in pre and perimenopausal women who did not receive Tamoxifen prior and ovarian ablation to those who received tamoxifen prior but have progressive disease [10]. Suh KJ et al. [11] in 2017 followed 66 patients with recurrent or metastatic disease who were premenopausal, HR+ve, HER2-ve and received aromatase inhibitors with GnRH agonists in 64% and BSO in 36%. Clinical benefit was higher (88%) in BSO group as compared with GnRH agonist (69%) group with a longer progression free survival period in BSO group [11]. Boccardo et al in 1998, reported higher incidence of side effects in GnRH group than in those who underwent oophorectomy [3]. In a latest study involving premenopausal metastatic breast cancer patients, seven of 13 patients who received

medical ovarian suppression stated that they would have chosen oophorectomy as a method of surgical ovarian suppression if it was offered to them at treatment initiation. A monthly painful injection with goserelin was a hassle which made BSO or surgical ovarian suppression as a prime choice [12]. However, Taylor and Hsieh AH demonstrated that both medical and surgical ovarian suppression were found to be effective and had similar overall survival rates. Goserelin was safe and well tolerated [13].

Suppression of Ovarian Function Trial (SOFT) is a 3-arm study comparing ovarian suppression with either tamoxifen or an aromatase inhibitor, exemestane, after surgery alone or surgery followed by chemotherapy, in premenopausal women with endocrine-responsive tumors. Tamoxifen and Exemestane Trial (TEXT) is compared ovarian suppression with either tamoxifen or exemestane with or without adjuvant chemotherapy. A third trial, Premenopausal Endocrine Responsive Trial (PERCHE) randomized patients to ovarian suppression plus tamoxifen or exemestane or to chemotherapy followed by ovarian suppression plus tamoxifen or exemestane. The inference of these studies was that in premenopausal cancer breast patients, adding ovarian suppression with tamoxifen had significantly higher disease-free and overall survival than giving tamoxifen alone. However the incidence of side-effects was more in groups that received ovarian suppression also. Addition of exemestane to ovarian suppression resulted in low rates of recurrence [14,15].

Table 1 depicts studies comparing various available treatment modalities and their outcomes in metastatic breast cancer. Randomized controlled trials by Ingle JN et al. [16], Buchanan RB et al. [17], Sawka et al. [18], were with few patients and in their analysis, tamoxifen and ovarian suppression had similar outcomes. In meta-analyses by Crump et al. [19], with more than 200 patients, the overall response rate, progression of disease and mortality rates were similar.

Using Tamoxifen for sequential hormonal therapy is beneficial in two ways. First a positive response to Tamoxifen predicts response with ovarian suppression and secondly, a better response is expected when ovarian suppression was used after tamoxifen in second line treatment. The Southeast Asian trial by Love et al. [20] enrolled 709 breast cancer patients with any receptor status. Patients were randomized before mastectomy to undergo either immediate oophorectomy or tamoxifen therapy versus observation until tumor relapses. Those with hormone receptor positive status had significantly higher disease free period, overall survival rates and response was much better in therapeutic arm rather than those with observation arm. This trial strongly supports the use of endocrine therapy in premenopausal women in hormone sensitive breast cancers.

Discussion

Around 10% of ovarian cancers and five percent of breast cancers occur due to germline mutations in BRCA1 and BRCA2 genes. Of these 26% to 34% are at risk for breast cancer and develop in their fifth decade of life [3]. Prophylactic BSO had significant risk reduction (90%) for developing ovarian cancer in these women thus suggesting reasonable, one-time and cost-effective option for adjuvant therapy in pre and perimenopausal hormone-sensitive tumors and an effective strategy for prevention of ovarian cancer [21,22]. Laparoscopy is the preferred method for performing a RRSO, due to a lower morbidity than laparotomy [23]. But there are no specific recommendations regarding BSO in women with non hereditary and disseminated carcinoma breast in premenopausal woman. In patients with

metastatic disease, endocrine therapy should be the preferred choice for hormone sensitive tumors. Tamoxifen and ovarian suppression/ablation is preferred over other drugs [24]. Tamoxifen has estrogen agonistic action on endometrium, ovary and has antagonist action in breast, thus treating breast tumors but increasing the risk of ovarian cysts, ovarian malignancy, endometrial hyperplasia and cancer.

The principle behind using chemotherapeutic agents in carcinoma breast is that they induce amenorrhea in premenopausal women by causing ovarian failure. Ovarian failure induced with these drugs is age related, with maximum effect seen in postmenopausal females as compared to younger women. Premenopausal woman who do not develop amenorrhea or have residual ovarian function after chemotherapy, benefits from additional ovarian suppression. If these women with residual ovarian function can be identified, BSO is a good alternative. With Aromatase Inhibitors /GnRHa there is theoretical risk of incomplete suppression of ovarian function [12,25].

Hormonal suppression with GnRH analogues was evaluated and effect was found to be similar to oophorectomy in few studies. The benefits of GnRH induced ovarian suppression are their reversibility and no surgery related complications. Current guidelines recommend monthly injections of GnRHa for two to three years and tamoxifen for five years or the combination therapy with both GnRH analogue and tamoxifen for 2 to 3 years and then replacing tamoxifen with aromatase inhibitor. High cost, compliance and their side effects are the disadvantages with GnRH analogues which is a matter of concern in developing countries [26]. Pros and Cons of each of these medical or surgical ablation therapies are to be discussed thoroughly before they are offered. With BSO there is maximum estrogen blockade and many studies reported a sense of well-being by these patients following a surgery. It has surgical morbidity with short- and long-term side effects and health consequences like vasomotor and urogenital symptoms, psychological effect on sexuality and body image, increased risk for osteopenia, osteoporosis, adverse cardiac events and cognitive dysfunction [26].

Laparoscopic BSO is cost effective to laparotomy with good cosmesis, shorter duration of surgery and in-hospital stay with earlier resumption to work and minor postoperative complications (0% to 6.1%). However, there is no one to one comparison and inference regarding side-effects, risk-benefit ratio, and morbidity with surgical and medical ovarian suppression. National Health Service recommended superiority of laparoscopic BSO over GnRH analogues [27]. The expenses incurred for cancer ovary prevention contributed only to 0.33% and 0.06% of the overall estimated cost for GnRH analogues and laparoscopic BSO, respectively. This sum amounts to much lesser attributes when compared with higher around 21% reduction in the risk of cancer ovary developments. Laparoscopic BSO in comparison to GnRH analogues had around 80% reduction in expenses [28].

Conclusion

In conclusion, achieving total ovarian blockade is a pivotal with metastatic breast cancer and most appropriate and efficacious method is to be individualized after complete clinical evaluation and counseling. Surgical ovarian ablation is cost-effective to medical therapy for adjuvant therapy with add on benefit of preventing ovarian cancer. However counseling regarding side-effects, risk-benefit ratio and quality-of-life after surgical menopause need to be addressed. The negative effect on quality-of-life and withdrawal symptoms after

surgical menopause can be partly balanced by improvement in anxiety associated with the risk of developing an ovarian cancer. Regardless of the analyses and results from various studies and trials, the physician's judgment and patients' choice after thorough counseling should be the decisive determinants.

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