www.jmscr.igmpublication.org Impact Factor 3.79
ISSN (e)-2347-176x

IGM Publication Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Treatment Modalities for Basal Like Breast Cancer

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ABSTRACT

Breast cancer represents a heterogeneous group of disorders with significant morbidity and mortality among female population. Basal like breast cancer represents one of the several sub types of breast cancer. It has always been considered synonymous to triple negative breast cancer but studies have repeatedly proven it and triple negative to be two separate entities having different immunohisto chemistry, clinical behavior and prognosis. Basal like breast cancer represents an immunophenotype similar to triple negative breast cancer in a respect that it lacks estrogen receptors (ER), progesterone receptors (PR) and human epithelial growth factor 2 (HER2) overexpression, but is quite distinct at the same time as it represents additional biomarkers as well like cytokeratins 5/6 and epithelial growth factor receptors (EGFR). Moreover, basal like breast cancers is characterized as tumors with greater degree of atypia, higher propensity of local invasion, easy distant metastasis and grim prognosis.

Even when it represent as much as 13-37% of breast cancer burden in young female population, definite treatment protocols remain lacking. Thorough analysis of currently available data in this regard has shown that breast conserving therapy (BCT) with adjuvant radiotherapy promises the best outcomes. In addition, pre-operative use of chemotherapeutic agents like paclitaxel followed by 5-fluorouracil, doxorubicin, and cyclophosphamide and post-operative use of anthracycline (doxorubicin/cyclophosphamide or

fluorouracil/doxorubicin/cyclophosphamide) and CMF based (Cyclophosphamide, Methotrexate, and Fluorouracil) adjuvant chemotherapy has shown to improve the prognosis. Furthermore, therapies that target features like dysfunction of BRCA1 and overexpression of EGFR are currently being studied as potential treatment options.

Key Words: *Breast Cancer, Basal Breast Cancer, Estrogen receptor (ER), Progestrone Receptors (PR), human epithelial growth factor 2 (HER2) overexpression, BRCA1, BCT, cytokeratins, epithelial growth factor receptors (EGFR).*

1. INTRODUCTION

While talking of female cancers, the first cancer that comes to mind is the cancer of breast. According to the American Cancer Society, at least one in eight women develops breast cancer during her lifetime [(1)]. Breast cancer represents a worldwide problem for females with significant morbidity and mortality. According to certain estimates, breast cancer accounts for 23% of all reported cancer cases in females. Moreover, it is responsible for at least 14% cancer related deaths in females worldwide [(2)]. In the US alone, almost 233,340 new cases of breast cancer were reported during the year 2013. Also, the toll of breast cancer deaths in the US during the year 2013 is expected to be 39,620 deaths [(1)]. Metastatic breast cancer represents a huge economic burden as well and people in the US spend almost $4.2 billion as direct and indirect expenses related to breast cancer treatment [(3)]. Due to the higher morbidity and mortality associated with breast cancer, it is vital to study the prognosis of this disease and its sub types in detail.

The presence of some or most of the etiological risk factors is generally associated with increased chances of development and poor prognosis of breast cancer [(4)].Variables pertaining to age are the most common risk factors for the development of breast cancer. The relative risk (RR) of breast cancer for different age related variables include: 12 years or younger at the time of menarche (RR; 1.3), onset of menopause at the age 55 years or older (RR; 1.2-1.5), first childbirth after the age 30 years (RR; 1.7-1.9), and current age of 65 or more (RR; 5.8) [(5)]. As for the geographical distribution, Western countries (including countries of the US and Europe) account for more than half of the total reported breast cancer cases [(6)]. Alcohol intake represents another important risk factor for breast cancer [(6)]. The relative risk for developing breast cancer by drinking 2 or more glasses of alcohol on daily basis is 1.2[(5)]. Dietary factors also influence the development of breast cancer. Eating a high caloric diet, especially rich in fats, significantly increase the risk of breast cancer. Whereas, eating a fiber rich diet is mildly protective against breast cancer [(7)]. Among women, the presence of central obesity greatly increases the risk of breast cancer [(8)]. Moreover, it has also been recognized that obesity and breast cancer prognosis are inversely linked [(9)]. Also, having a family history of breast cancer greatly increases the risk for developing this condition before the age of 50 years [(10)]. As for the link

between endocrine system and breast cancer, elevated level of estrogen and progesterone has been linked with increased risk of breast cancer [11][12]. Finally, presence of certain pre-existing breast disease (like fibrocystic breast disease) [13]; mammographic breast densities [14]; treatment with hormone replacement therapy (HRT) [15]; and exposure to ionizing radiations [16] are all well recognized risk factors of breast cancer.

Breast cancer represents a heterogeneous disorder containing multiple entities that differ in their immunophenotype, morphology and clinical behavior [17]. Based on molecular patterns, four subtypes of breast cancer have been identified: normal breast like, luminal, HER2 and basal like [18]. Among these subtypes, none has proved to be as interesting and as controversial as basal like group and this subtype of breast cancer has been extensively studied in the recent past [19]. By far, there is no set definition that could give an in-sight about the structure and behavior of this cancer. However, based on the immunohistochemical markers, basal like breast cancer may be defined to have following features: (i) triple negative immunophenotype with the lack of expression of estrogen receptors (ER), progesterone receptors (PR) and human epithelial growth factor receptor 2 (HER2); (ii) basal like breast cancers also express additional biomarkers like either single or multiple basal cytokeratins, including CK5/6, CK14 and CK 17 and epithelial growth factor receptor (EGFR); (iii) Cheang et al, defined a sub type of basal like breast cancer and named it core basal that was found to be ER (-), PR (-), HER2 (-) and positive in either cytokeratins 5/6 (+) or EGFR (+). Although HER1 is not typically considered a marker for basal like breast cancer but Neilsen et al, found this marker in enough basal cells to combine it with other markers: HER1 (+), HER2 (-), cytokertains 5/6 (+) and ER (-); [20][21] (iv) basal like breast cancers defined by the expression of five biomarkers, also called 5 negative phenotype (5NP): ER (-), PR (-), HER2 (-), cytokeratin 5/6 (-) and epithelial growth factor receptors (EGFR) (-)[21] (Table 1). Moreover, mutation in BRCA-1 genes is also very common in these types of breast cancers [19].

As mentioned before, basal like breast cancers usually express a triple negative immunopheno type. This sprouts a question if basal like breast cancer and triple negative breast cancers are synonymous? Until recently, both terms have been used interchangeably and were thought to represent a single sub type of breast cancer [22] [23]. While it is true that most of the triple negative breast cancers show a phenotype resembling basal like cancers [22] [24] [25] and most of the basal like tumors show a triple negative immunophenotype [22] [25] [26] . But this cannot be generalized i.e. all basal like breast cancers don't always lack ER, PR and HER2 and all triple negative breast cancers don't always show a basal like phenotype [27] [28] [29]. Kreike and colleagues studied the pathological and genetic features of 97 cases of triple negative invasive breast cancers. As expected, almost 91% cases of triple negative breast cancers were of basal like variety. However, remaining 9% had normal like or unclassifiable phenotype [23]. Similarly, Bertucci et al showed by the results collected through gene profiling that only 71%

triple negative tumors have a basal like character and only 77% basal like breast cancers show a triple negative immunophenotype[26]. Not only that but triple negative tumors do not always show histological similarity with basal like phenotype, as is demonstrated by a variety of breast cancers including pleomorphic lobular carcinoma, certain varieties of mixed duct lobular carcinoma and apocrine cancer [23] [30].

Apart from their genetic heterogeneity, another important factor making them even more diverse is their varied histological presentation. Researchers have found that most of the basal like breast cancers are grade 3 tumors representing histological features of atypia including abundant mitotic figures, central (geographical) zones of necrosis and fibrosis, invasion of stroma by lymphocytes, greater degree of nuclear pleomorphism, pushing margins of infiltration and scarcity of tubule formation [31] [32] [33]. Most of the basal like breast cancers are intra-ductal carcinomas with no specific type (IDC-NST) but sometimes other types of breast cancer also do histologically resemble basal like breast cancers, such cancers include: medullary and atypical medullary breast cancers [34], secretory [35], adenoid cystic carcinoma [36], metaplastic[37] and myoepithelial type breast cancer [36] (Table 2). In addition, basal like breast cancers are highly aggressive tumors characterized by greater degree of local invasion, early metastasis and extremely poor prognosis especially after metastasis [38] [39].

Taken together, basal like breast cancer represents an important yet heterogeneous sub type of breast cancer with prevalence ranging from12.3–36.7% in different patient cohorts [40]. Comparison between basal like breast cancer and luminal type A (the most common type breast cancer) shows that basal like breast cancer differs from other breast cancers in several ways. Results of a population based, case control study conducted on African American female population showed that the risk of basal like breast cancer increases significantly with increased parity and younger age at the time of first pregnancy. These observations are opposite to those observed for luminal A breast cancer [41]. In short, basal like cancer is more common in younger females and females belonging to African American descent[19].

In a crux, basal like breast cancer represents a significant burden of breast cancer; possesses perplexing heterogeneity both in morphology and genetics; is invasive in character; undergoes metastasis early and is generally believed to have poor prognosis. Therefore, the purpose of this review article is to determine the effectiveness of different treatment modalities that are currently being used for the management of this heterogeneous sub type of breast cancer. Towards the end, this paper will also discuss some of the future therapies that are under investigation and might prove useful in the treatment of this sub type breast cancer.

2. DISCUSSION

Exploration of treatment modalities for different type breast cancers is a matter of ongoing and intense clinical research. In the contemporary management of breast cancers, different options

are available for the regional or local treatment of breast related cancers. The selection of the right treatment option is very critical for an oncologist because several factors like the relapse, morbidity and mortality of the patients depend on the accurate treatment choices made. Since basal like breast cancer represents an aggressive, atypical and locally invasive tumor that can easily undergo metastasis to distant sites and shows grim prognosis, so there is a need to explore and compare different treatment modalities for the management of this resilient breast cancer type. Therefore, in this section we've explored different treatment options that are currently being used for the management of basal like breast cancer.

2.1. Breast conserving therapy vs. Breast conserving therapy with adjuvant radiotherapy vs. Mastectomy vs. Mastectomy with adjuvant radiotherapy.

Is breast conserving therapy (BCT) with adjuvant post-operative radiotherapy any superior to BCT alone when it comes to the surgical approach for the treatment of basal like breast cancer? Ewan et al and colleagues showed that five year local recurrence rate (LRR) in patients undergoing BCT alone was the highest among patients with basal like breast cancer in comparison to other breast cancer subtypes. The LRR for basal breast cancer group undergoing BCT with no adjuvant therapy was determined to be as high as 14.8% [(42)]. In comparison, the five year LRR for patients receiving BCT and radiations came out to be only 7.1% in another study [(43)]. This comparison shows that BCT with adjuvant radiotherapy provides more favorable therapeutic outcomes as compared to BCT therapy alone (Table 3).

Do mastectomy and mastectomy with adjuvant radiotherapy come with any clinically different outcomes? Kydi et al showed that postoperative radiotherapy after mastectomy doesn't give statistically significant benefit over mastectomy alone [(44)].

Finally, is BCT with adjuvant radiotherapy superior to mastectomy as well? Voduc et al and colleagues studied the patterns of local and regional relapse in females with different sub types of breast cancer after they were treated with either mastectomy or BCT with adjuvant radiotherapy. The cohort consisted of 2,985 females that were diagnosed with 6 different breast cancers: luminal A, luminal-HER2, luminal B, tumors rich in HER2, basal like cancer and triple negative-non basal breast cancers. The patients were either treated with breast conserving therapy (BCT) followed by adjuvant radiotherapy or mastectomy. The efficacy of the treatment modalities employed was judged by a 12 year follow up where variables like local and regional relapse of the tumors was determined. Statistical analysis of the results showed that BCT with adjuvant radiotherapy was superior to mastectomy for the treatment of basal like breast cancer because the local relapse free survival (LRFS) was 86% among the patients who underwent BCT followed by adjuvant radiotherapy as compared to 81% in patients who underwent mastectomy. Moreover, 10 year regional relapse free survival came out to be 86% and 80% for BCT with radiotherapy and mastectomy groups

respectively[45](Table 4). This shows that BST followed by adjuvant radiotherapy is superior to mastectomy alone for the treatment of grade 3 basal like breast cancers.

2.2 Chemotherapy

Cheang et al, described that patients with 5NP immunophenotype generally have better prognosis and show 26% better 10 year breast cancer death specific survival (BCSS) upon treatment with anthracycline-based adjuvant chemotherapy (doxorubicin/cyclophosphamide or fluorouracil/doxorubicin/cyclophosphamide) as compared to core basal patients treated with similar regime [21]. Similar results were obtained from another study that showed that core basal varieties respond less effectively to anthracycline based chemotherapy [46]. As for the core basal variety, women with this type breast cancer respond better to CMF based adjuvant chemotherapy (Cyclophosphamide, Methotrexate, and Fluorouracil) as compared to anthracyline based chemotherapy [47][48] (Table 5).

HER1 (+) basal like breast cancers, as described by Nielsen et al, open a new perspective for the treatment of basal like breast cancers. HER1 is the target of antibodies like cetuximab and tyrosine kinsase inhibitors like erlotinib and gefitinb[20][49][50]. These drugs might also prove valuable in the treatment of basal like breast cancer.

Pre-operative regimes can also be employed for basal like breast cancer. Rouzeir and colleague studied the effects of pre-operative chemotherapy regime containing paclitaxel followed by 5-fluorouracil, doxorubicin, and cyclophosphamide on different sub types of breast cancer. Results showed that basal like breast cancer responded best to this pre-operative chemotherapy regime as compared to other breast cancer sub types [29] (Table 5).

The data obtained from all these studies is still preliminary to give any conclusive remarks regarding the chemotherapy options best suited for basal like breast cancer. Therefore, more research is warranted in this area.

2.3 Future Perspective

2.3.1 Drugs targeting defect in DNA repair

BRCA1 mutation is common in basal like breast cancer [19]. BRCA1 functions to promote DNA repair and thus uplifts cellular integrity. However, mutations in this gene can cause DNA repair deficits and can thus make the cells susceptible to the action of targeted chemotherapeutic agents [51][52]. Results of clinical trials have shown that cells having defect in BRCA1, such as basal like breast cancer, are highly sensitive to the DNA damaging effects of platinum salts [53].

2.3.2 Poly (ADP-ribose) polymerase (PARP1) inhibitors

Poly (ADP-ribose) polymerase in an important enzyme that works in conjunction with BRCA1 to mend mutations in the DNA structure [54]. A number of Poly (ADP-ribose) polymerase (PARP1) inhibitors, like veliparib, olaparib and iniparib, are being tested clinically for their cytotoxic effects on the cells lineages with mutated BRCA1 genes. Results of one such experiment have shown that patients with mutated BRCA1 gene have as much as 41% response rate to the oral intake of olaparib[55].

2.3.3 Anti-angiogenic drugs

Till date it is unclear if the response of basal like breast cancers is any superior to other type breast cancers when it comes to the treatment with anti-angiogenic agents [56]. VEGF is expressed approximately 3 folds higher in triple negative/basal like breast cancers as compared non triple negative/basal like breast cancers [37][57]. Theoretically, triple negative and basal like breast cancers should respond to anti-angiogenic drugs targeting VEGF. There has been some preliminary evidence that treatment with paclitaxel (with and without bevacizumab- an antibody directed against VEGF); bevacizumab along with cisplatinumorsunitinib (a VEGFR inhibitor) can benefit the patients with triple negative and basal like breast cancers [58][59][60].

2.3.4 EGFR inhibitors

Basal like breast cancers are positive for additional biomarkers, one of which is EGFR [19][20]. There has been some evidence where giving cetuximab, an antibody targeted against EGFR, alone or in combination with carboplatin produced moderate antitumor activity in triple negative/basal like breast cancer [61].

2.3.5 Miscellaneous drugs

Other agents being tested for their benefits in the treatment of basal like breast cancer include inhibitors of ABL and SRC family kinases (like dasatanib) [62][63][64] and inhibitors of pathways associated with lymphocytic activation in basal like breast cancer [56].

Table 1: Features of basal like breast cancer based on immunohistochemical markers.

Subtype of Breast Cancer	Expression of ER, PR and HER2	Additional Biomarkers	Basal like cancers defined by four markers (Core basal)	5 negative marker phenotype (5NP)
Basal like	ER (-) PR (-) HER2 (-)	Cytokeratins 5/6 (+) EGFR (+)	ER (-) HER2 (-) HER1 (+) Cytokeratins 5/6 (+) or EGFR (+)	ER (-) PR (-) HER2 (-) Cytokeratins 5/6 (-) EGFR (-)

Table 2: Histological features and types of basal like breast cancer

Subtype of breast cancer	Histological Features	Histological special types
Basal like	Presence of mitotic figures, geographical necrosis or fibrosis, greater degree nuclear pleomorphism, stromal invasion by inflammatory cells, lesser degree of tubule formation.	-IDC-NST -Medullary and atypical medullary -Secretory -Adenoid cystic carcinoma -Metaplastic -Myoepithelial

Table 3: Comparison of five year LRR in patients with basal like breast cancer undergoing BCT alone or BCT with radiotherapy.

Procedure	Five year LRR
BCT	14.8%
BCT with adjuvant radiotherapy	7.1%

Table 4: Comparison of 10 year LRFS and RRFS in patients with basal like breast cancer treated with mastectomy or BCT with adjuvant radiotherapy (Voduc et al, 2010)

Procedure	**No. of patients**	**No. of patients with ten year recurrence**	**10 year relapse free survival(%)**
10 year Local Relapse Free Survival (LRFS)			
Mastectomy	161	26	81%
BCT with radiotherapy	134	19	86%
10 year Regional Relapse Free Survival (RRFS)			
Mastectomy	161	27	80%
BCT with radiotherapy	134	17	86%

Table 5: Pre and post-operative chemotherapy options for basal like breast cancer

Type of Chemotherapy	**Drug regime**
Pre-operative chemotherapy	Paclitaxel followed by 5-fluorouracil, doxorubicin, and cyclophosphamide
Post-operative chemotherapy for 5NP variety	Anthracycline-based adjuvant chemotherapy (doxorubicin/cyclophosphamide or fluorouracil/doxorubicin/cyclophosphamide)
Post-operative chemotherapy for core basal variety	CMF based adjuvant chemotherapy (Cyclophosphamide, Methotrexate, and Fluorouracil)

3. CONCLUSION

To conclude, basal like breast cancer is still an underestimated and understudied sub type of breast cancer having grim clinical outcomes. It represents a significant burden of breast cancer cases but the treatment options are still not clearly defined. In this review we analyzed currently available data in this regard and came to the conclusion that BCT with adjuvant radiotherapy; pre-operative use of chemotherapeutic agents like paclitaxel followed by 5-fluorouracil, doxorubicin, and cyclophosphamide and post-

operative use of anthracycline (doxorubicin/ cyclophosphamide or fluorouracil/ doxorubicin/ cyclophosphamide) and CMF based (Cyclophosphamide, Methotrexate, and Fluorouracil) adjuvant chemotherapy has shown the best promise in the treatment of this resilient variety of breast cancer. Still, the available data is preliminary to state anything conclusively and more research needs to be done in this area to further improve the available treatment options for patients having this sub type breast cancer.

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