Effect of Basal Subtype in Survival in Metastatic Breast Cancer Patients who Received First-Line Gemcitabine-Carboplatin after Receiving Anthracyclines and Taxanes in Adjuvant Phase

Abstract

To assess the effect of basal subtype in survival in patients with metastatic breast cancer who received first-line gemcitabine\carboplatin.

Patients & Methods: The basal subtype status was determined by using the basal cytokeratin markers CK5/6. Eligible metastatic tripe negative breast cancer (MTNBC) women with prior adjuvant treatment by anthracyclines and taxanes were enrolled to receive carboplatin AUC 5 in day1 and gemcitabine 1gm/m^2 on day1 and 8 for up to 6 cycles, until disease progression or unacceptable toxicity. End points were progression-free survival and overall survival in patients with basal and non-basal subtype.

Results: Thirty-three patients of MTNBC presented in a period from February 2013 to March 2015 were treated with gemcitabine\carboplatin. Patients had a median age of 43.6years (range, 24-71 years, S.D: 11.161)23 patients were premenopausal (69.7%) & 10 patients were postmenopausal (30.3%). Approximately 81% of patients had a good PS (0-1). 12 patients were basal subtype (positive ck5/6) from twenty patients who had accessible specimens for examination of cytokeratin (12out of 20=60%), Mean overall survival (OS) in patients has basal subtype were 12 months, while in patients has non-basal subtype were 12.96 months (95% CI-3.53-5.45) P<0.242). Median progression-free survival (PFS) in basal subtype were 5.857 months while in non-basal subtype were 6.15 months (95% CI-1.79738-2.39079) P<0.456).

Conclusion: Post metastatic presentation, the OS and PFS was slightly lower among patients with basal subtypes compared to non-basal subtypes; however this difference in PFS and OS between the two groups did not reach statistical significance.

Keywords: Basal; TNBC; Metastatic; HER2/Neugene; Cytokeratins; Immunohistochemistry

Research Article

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Introduction

Triple-negative breast cancers (TNBCs), those that do not express estrogen, progesterone receptors and *HER2/Neu*gene, Approximately 15-20% of all breast cancers account for TNBCs that exhibit aggressive, distinct metastatic pattern and poor prognosis, more than 50% of patients with TNBCs develop early relapse and shorter survival [1]. Recent studies using gene expression profiling and immunohistochemistry have identified a distinct subset of breast tumours that exhibit a basal phenotype or express a gene expression signature that includes a relatively high level expression of stratified epithelial/basal cytokeratins (CK5/6 and CK14) [2] TNBC is molecularly a heterogeneous disease. Most basal-like breast cancers (~80 %) are of the triple negative phenotype. recently, TNBC has been divided into six distinct subtypes:

A. Immunomodulatory
B. Mesenchymal
C. Mesenchymal stem-like
D. Luminal androgen receptor
E. Basal-like
F. Basal-like 2 [3]

More recently Baylor molecular classification of TNBC identified and confirmed four distinct TNBC subtypes after genomic profile for RNA and DNA:

a) Luminal androgen receptor (AR; LAR)
b) Mesenchymal (MES)
c) Basal-like immuno suppressed (BLIS)
d) Basal-like immune-activated (BLIA)

Of these, prognosis is worst for BLIS tumors and best for BLIA tumors for both disease free survival (DFS) and disease-specific survival (DSS). DNA copy number analysis produced two major groups (LAR and MES/BLIS/BLIA) and suggested that gene amplification drives gene expression in some cases [FGFR2 (BLIS)]. Putative subtype-specific targets were identified:

a. LAR: Androgen receptor and the cell surface mucin MUC1

b. MES: Growth factor receptors [platelet-derived growth factor (PDGF) receptor A; c-Kit]

c. BLIS: An immuno suppressing molecule (VTCN1)

d. BLIA: Stat signal transduction molecules and cytokines [4]

Patients and methods

Study methods

Inclusion criteria:

A. Age ≥ 18 years.

B. Eastern Cooperative Oncology Group Performance status (ECOG) of 0-2.

C. Histologically confirmed carcinoma of the breast with triple negative ER, PR and Her -2 on primary breast cancer specimens and metastatic breast carcinoma with measurable disease & cytokeratin (5/6) for a basal type.

D. Adequate hematopoietic, hepatic, renal and cardiac functions, a negative baseline pregnancy test.

E. Prior chemotherapy apart from adjuvant chemotherapy not includes platinum or gemcitabine.

F. Patients received taxanes in neoadjuvant or adjuvant line.

Methodology in details: Each patient gave a written informed consent, and the following pretreatment evaluations were performed: medical history, physical examination, vital signs, height and body weight and ECOG performance status. Radiological measurements (Computed tomography (CT) chest, abdomen and pelvis, bone scan and any other images were done when appropriate), complete blood with differential and platelet count, hemoglobin, and chemistries, hepatic and renal function CA15.3.

Treatment protocol: All patients received combination chemotherapy as carboplatin area under the curve (AUC) 5 in day1 and gemcitabine 1gm/m^2 on day1 and 8, treatment were repeated every 3 weeks. Treatment was administered until progression or unacceptable toxicity, patient's refusal or for a maximum of 8 cycles. Antiemetic prophylaxis was given before chemotherapy according to the local protocols including 5 hydroxythreonine 3(5HT3) antagonists and dexamethasone. Both drugs were delayed as long as there was grade 1 or greater toxicities, neutropenia <1500 per µl or thrombocytopenia <100, 000 per µl. Also, both drugs were reduced by 25% of the previous dose in case of grade 3/4 toxicities.

Efficacy assessment

The primary objectives of the study were to estimate the progression-free survival and overall survival in patients with basal and non-basal subtype. Pretreatment evaluation includes history and physical examination, complete blood cell count with differentials, chemistry, CT scan of chest abdomen and pelvis, bone scan and any other diagnostic procedures as clinically indicated. During treatment, a history taking, physical examination including toxicity assessment, complete blood cell count and chemistry were carried out every 3 weeks before each cycle. Appropriate imaging studies including chest, abdominal, and pelvis CT scan were carried out every 3 cycles (9 weeks) to evaluate treatment response, or sooner if needed for documentation of disease progression. Responses were confirmed by subsequent CT scans 9 weeks after the initial response documentation. Patients were assessed every 3 months for disease progression following the completion of the chemotherapy. Responses were classified according to RECIST criteria. TTP was calculated from the first day of treatment to the date on which disease progression was first documented or of the last follow-up. OS was calculated from the first day of treatment to the date of death or last follow-up. Toxicity was monitored according to the National Cancer Institute common toxicity criteria (NCI-CTC).

Sample size (number of participants included)

The expected number of patients for this study is calculated according to a Simon optimal two stage design. An interim analysis was carried out if over three patients among the first 17 patients have objective response; this study is regarded to be adequate to proceed further and to enroll more 17 patients assuming P0 of 15%, P1 of 35%, α-error of 0.05 and B-error of 0.20. Thirty four eligible patients are required to evaluate the activity of this combination**.**

Results

Thirty-three patients of MTNBC presented in a period from February 2013 to March 2015 were treated with gemcitabine\ carboplatin. Patients had a median age of 43.6years (range, 24-71 years, S.D: 11.161)23 patients were premenopausal (69.7%) & 10 patients were postmenopausal (30.3%). Approximately 81% of patients had a good PS (0-1). 12 patients were basal subtype (positive ck5/6) from twenty patients who had accessible specimens for examination of cytokeratin (12out of 20=60%), Mean overall survival (OS) in patients has basal subtype were 12 months, while in patients has non-basal subtype were 12.96 months (95% CI-3.53-5.45) P <0.242). Median progression-free survival (PFS) in basal subtype were 5.857 months while in non-basal subtype were 6.15 months (95% CI-1.79738-2.39079) P <0.456).patient had complete response (CR) Figure 1.

Toxicity

Hematologic toxicity

It was neutropenia grade one in 15\33 patients (45.5%) neutropenia grade two, 10\33patients (30.3%), anemia grade one reported in 9\33 patients(27.3%) anemia grade two reported in 12\33 patients (36.4%), anemia grade three in 1\33 patients(3%), thrombocytopenia grade one reported in 13\33patients (39.4%) thrombocytopenia grade two reported in 1\33 patients (3%).

Non- hematologic toxicity

GIT: Vomiting, usually grade one 10 patients (30.3%) & nausea in 11 patients (33.3%).

Nutrition: Anorexia grade one presented in 7 patients (21.2%) and grade two in 5 patients (15.1%)

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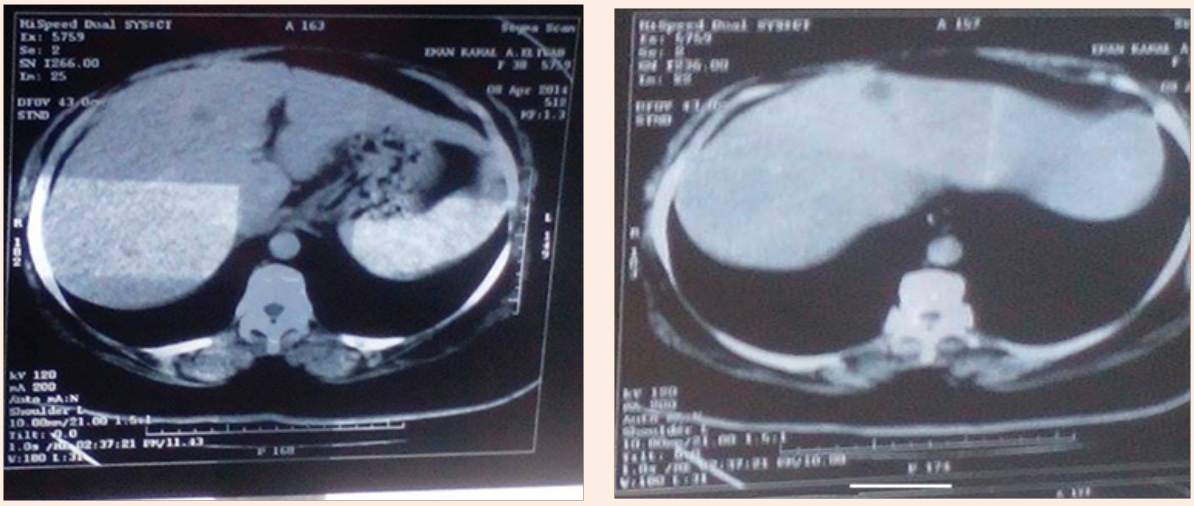

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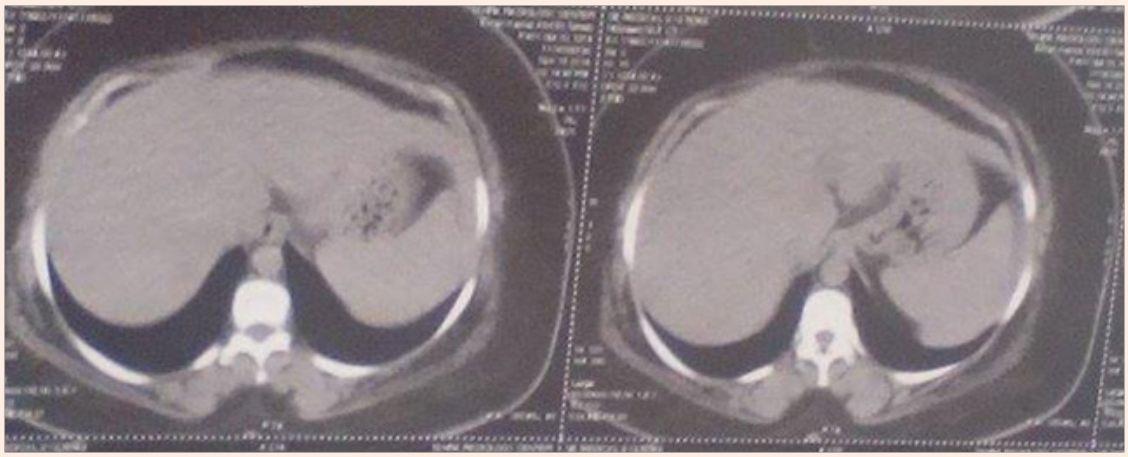

Figure 1: Liver metastasis, a. Before treatment & b. After treatment.

General: Fatigue grade one presented in 10 patients (30.3%) and grade two in 4 patients (12.1%).

Chest: Dyspnea grade one presented in 16 patients (48.4%) and grade two in 5 patients (15.1%).

CNS: Headache in 13 patients (39.4%) convulsions in 3 patients (9%).

Musculoskeletal: Bony pain grade one presented in 13 patients (39.4%) and grade two in one patient (3%). Toxicities are summarized in Tables 1 & 2.

Discussion

The molecular signature of triple-negative breast cancer generally overlaps with basal-like breast cancer, with concordance of 70-90%. In this study twelve patients out of twenty patients who had accessible specimens were basal subtype 60% (12/20), this is more than reported by Zhang J et al. [5] 48.6% (18 of 37) were BLBC. In this study median overall survival (OS) in patients has basal subtype were 12 months; while in patients has non basal subtype were 12.9 months P<0.242). this is more than reported by Kennecke H et al. [6] showed that It was just 5 months for BLBC and 9 months for non- basal subtype, and near that was done by Luck AA et al. [7] in the basal group was 10.1 months, compared with 25 months non basal phenotype. (P<0.001)and less than reported by Zhang J et al. [5] median OS was 40.3 in BLBC and 14.7 months in non-BLBC subtypes (p<0.04).

In this study median progression free survival (PFS) in basal subtype were 5.8 months while in non-basal subtype were 6.1 months (P<0.456) this is less than reported by Zhang J et al. [5] median PFS was 12.9 months for the BLBC subtype and 5.6 months for non-BLBC subtype (p<0.002) however we cannot compare between the basal and non-basal in the present study as not all the patients have specimens to do cytokeratin and also the small sample size of the study group. The different of the results among these studies using the same regimen may be related that TNBC is not single disease but is heterogonous subtypes with different biological characters [8].

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Table 1: Patient characteristics.

Characteristic	NO (%)
Number of Patients	33
Age (Years)	
Median	43.6
Range	24-71
Menopausal Status	
Premenopausal	23(69.7%)
Postmenopausal	10(30.3%)
Performance Status	
0	2(6.1%)
1	25(75.8%)
2	6(18.2%)
Metastatic Disease Sites	
Liver	15(45.5%)
Lung	21(63.6%)
Bone	9(27.3%)
Brain	4(12.1%)
Lymph nodes	6(18.2%)
Local	3(9.1%)
Number Of Metastatic Sites	
1	11(33.33%)
2	18(54.54%)
3	4(12.1%)
Ck56/	
Positive	12 out of 20 (60%)
Negative	8 out of 20(40%)
Not Identified	13(39.4%)

Table 2: Side Effects.

Side Effects	Grade 1	Grade 2	Grade 3
Anemia	9(27.3%)	12(36.4%)	1(3%)
Neutropenia	18(54.5%)	10(30.3%)	0
Thrombocytopenia	13(39.4%)	1(3%)	0
Vomiting	10(30.3%)	0	0
Nausea	11(33.3%)	0	0
Bony pain	13(39.4%)	1(3%)	0
Fatigue	10(30.3%)	4(12.1%)	0
Dyspnea	16(48.4%)	5(15.1%)	0
Headache	13(39.4%)	0	0
convulsion	3(9%)	0	0
Anorexia	7(21.2%)	5(15.1%)	0

It is known that HER2-negative metastatic breast cancer would benefit from maintenance therapy in terms of both progression-free survival and overall survival after the publication of the KCSG-BR07-02 trial [9], However, even with the publication of results from this trial, most guidelines for breast oncology discourage maintenance strategy with chemotherapy for stage IV breast cancer, because of the toxic effects in a setting without evidence for curability. Additionally, maintenance chemotherapy has many unresolved issues, such as the choice of combination versus monotherapy, oral versus intravenous delivery, and others. The tolerability profile of carboplatin plus gemcitabine combination was as expected in our study, and when compared with the scientific literature, no new safety concerns were identified. Adverse effects in this study was acceptable and manageable most serious side effects were neutropenia G3 in 3 patients(9%) one of them developed febrile neutropenia, anemia grade three in 4\33 patients(12%),thrombocytopenia grade 3 in 5 patients (15%). Fatigue grade two in 4 patients, Dyspnea grade two in 5 patients, Bony pain grade two in one patient. Limitation of this study was the limited number of patients and this was due to eligibility criteria that all patients had received previous neoadjuvant or adjuvant chemotherapy in the form of anthracyclines and taxanes.

Conclusion

Post metastatic presentation, the OS and PFS was slightly lower among patients with basal subtypes compared to non-basal subtypes; however this difference in PFS and OS between the two groups did not reach statistical significance.

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