The Assessment of Response to Adjuvant Chemotherapy with CMF in Triple Negative Breast Cancer

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ABSTRACT

Introduction: Breast cancers are divided into at least 4 sub Types on the Basis of gene expression profiles and expression of receptors as measured by IHC (Immunohistochemical). Triple negative breast cancer (TNBC) is more chemosensitive yet. It is much harder to detect than other sub types. At present lack of highly effective therapeutic targets for TNBC, standard chemotherapy is the only medical treatment but it is not remarkably efficient. CMF (cyclophosphamide-MTX-5-fu) chemotherapy is effective in some sub types of TNBC.

Patients and methods: A Total of 40 patients with TNBC who had undergone surgical resection because of primary Invasive Breast cancer were studied from 2009 to 2011. Twenty patients in treatment group received four cycles of modified CMF after standard chemotherapy and 20 patients in group control received standard chemotherapy (antracycline/taxane), patients were regularly followed up every 3 months for median observation 13.3 months.

Results: In our study the prevalence of TNBC was %13.5. The average age of patients was 49.5 years. Their clinical and histopathological characteristics include: 90% Invasive Ductal carcinoma, 55.35% LN(Lymph node) pos, 61.3% P53 Pos, 74.5% Ki67 ≥ 20, 68% grade III. There was No statistical differenced between control and treatment group in OS and DFS Followed up 13.3 months.

Conclusion: The results of study indicate that the adjuvant therapy with regimen CMF in TNBC patient after standard chemotherapy with antracyline / taxane- Base no affected out come in patient in Median follow up 13.3 months.

KEY WORDS: Chemotherapy, CMF, TNBC

INTRODUCTION

Breast cancer is a heterogeneous disease in gene expression, morphology, clinical course and response to treatment.

Gene expression profiling and IHC tests can be used to classify breast cancer into four subtypes. Triple-negative breast cancer is one of these subtypes, which is defined as the absence of estrogen and progesterone receptor expression (ER and PgR) as well as human epidermal growth factor receptor 2 (HER2). Triple-negative breast cancers comprise about 10–27% of all breast cancers. This subtype is more aggressive from the clinicopathological point of view. It affects more frequently young women and presents with higher stage of disease, leading to visceral metastases versus osseous. Women with triple-negative breast cancer have poorer survival and there is no approved targeted therapy for triple-negative breast cancer. Cytotoxic chemotherapy remains the
mainstay of treatment for TNBC. Many studies have reported on the usefulness of this therapy. Neoadjuvant therapy is effective in TNBC patients than in non-TNBC which cause their long recovery. TNBC heterogeneous disease has many sub types such as: sub Type with Mutation BRCA1, sub Type basaloid, sub Type with mutation pro retinoblastoma with good response to CMF regimen. Due to more sensitive to DNA damage agent effective to pathway thymidylate synthase, antracyclines and taxanes that these drugs have verified effect. Platinumes have these effects. Yet in these patients Regimen containing taxanes and antracyclines remains as important medicinal regimen but was not more exclusive than non-TNBC patients. 1-3

The purpose of this study was thus, to investigate the effects of taxanes/antracyclines with CMF chemotherapy.

MATERIALS AND METHODS

This interventional clinical trial was performed on patients with stage I-III breast cancer. Twenty patients with TNBC were analyzed from May 2009 to June 2011. All patients had surgery in order to primary invasive breast cancer. They were under chemotherapy with antracycline/taxane Base. Then they received four cycles of modified CMF. Patients were allowed to receive radiation following completion of chemotherapy. The median follow-up in the treatment group was 13.3 months (range: 8-24 months). Twenty TNBC patients in the control group underwent anthracycline- or taxane-based chemotherapy following surgery. The patients' information is illustrated in Table 1. Patients were included in the study if they met the following criteria: over age 18, identified as a new case and negative for metastases (stage I-III). The patients with abnormal liver and renal function tests and cardiac dysfunction were excluded the study.

Statistical Methods

Data analysis was performed using SPSS16. Descriptive statistics such as frequency, percentage, mean and SD as well as inferential statistics such as t-test, Chi-square and Fisher’s exact test were used to analyze data. The level of significance was defined as p ≤ 0.05. The sample size was 20 participants.

| Table 1: Characteristic Clinical and Pathological in TNBC Patients |
|---------------|------------------|------------------|
| Variable      | Case n (%)       | Control n (%)    |
| Age ≤50       | 11(55%)          | 12(60%)          |
| >50           | 9(45%)           | 8(40%)           |
| Histological Diagnosis |
| Ductal carcinoma | 18(90%)         | 1(5%)            |
| Labular carcinoma | 1(5%)           | 20(100%)        |
| Medullary carcinoma | 1(5%)          | 20(100%)        |
| Mucoid carcinoma |                |                  |
| Tumor size    |
| pT1           | 3(15.8%)         | 2(10%)           |
| pT2           | 13(68.4%)        | 17(85%)          |
| pT3           | 3(15.8%)         | 1(5%)            |
| pT4           | 0(0%)            | 0(0%)            |
| Histologic grade |
| G1            | 0(0%)            | 0(0%)            |
| G2            | 7(35%)           | 9(45%)           |
| G3            | 13(65%)          | 11(55%)          |
| Nstatus No    | 10(55%)          | 6(33.3%)         |
| N+            | 8(44.4%)         | 12(66.7%)        |
| PS3 LI Positive | 10(52.6%)       | 14(70%)          |
| Negative Ki67 | 9(47.4%)         | 6(30%)           |
| <20%          | 6(35.3%)         | 3(15.8%)         |
| ≥20%          | 11(64.7%)        | 16(84.2%)        |
| Adjuvant Therapy |
| Radiotherapy  | 20(100%)         | 20(100%)         |
| Chemotherapy  | 20(100%)         | 20(100%)         |

RESULTS

The mean age in the treatment and control groups was 50 and 48 years, respectively. The mean age of patients was 49.5 years (range: 29-63). 90% and 44% of patients had ductal carcinoma and positive LN, respectively. In the control group, 66.7% of the participants had positive LN. Regarding tumor size, T1, T2 and T3 were 15.6%, 68%, 15.8%, respectively in the treatment group. In the control group, T1, T2 and T3 were 15.6%, 85% and 5%, respectively. In total patients, T1, T2 and T3 were reported 12.9%, 76.4% and 10.4%. Ki67≥20 was 35%, 15.8% and 25.4% in the treatment group, control group and total patients, respectively. P53 was 52.6% in the treatment group, 70% in the control group and 61.3% in total patients. Tumor grades including I, II and III were found to be 0%, 35% and 65%, respectively in the patients and 0%, 45% and 55%, respectively in the control group.
It is worth mentioning that one patient after four months of chemotherapy developed skin and liver metastases, which was the cause of her death after 6 months of treatment. Another patient in course 2 of CMF was affected by grade III nausea and vomiting which caused to stop the treatment. From 20 patients in control groups one patient was affected by bone metastasis. There was no significant difference in OS, DFS between two groups.

**DISCUSSION**

TNBC cancers have more aggressive behavior and worse prognosis. They have medical strategy and are less preventive than cancers with hormonal receptor positive.\(^6\) \(^7\) in the present study the prevalence of this subtype was 13.5%. The mean age of patients was 49.5 years. 60% of patients had high histologic grade (gradeIII). 55.35 % of patients had positive LN, 76.5% T2 tumor, 9% ductal carcinoma, 61.3% p53 positive and ki-67>20 was seen in 74% of patients. The results of this study are similar to those obtained by Ytaka et al. (2010), in which the prevalence of TNBC was reported 11-17%. The mean age in TNBC and non-TNBC groups was 53 and 57 years, respectively. In the study of TNBC patients, LN metastasis, average tumor size, p53 positive cells, high histologic grade and 60 ki-67>30 were 57.7%, 3 cm, 71%, 68% and 60%, whereas in non-TNBC patients were46%, 1cm, 14.2% and 16%, respectively.\(^1\) In another study by Di Leo et al., in patients with TNBC, anthracycline-based therapy was superior to CMF in terms of DFS with borderline statistical significance which was not comparable with our study.\(^5\) Trail tact that was performed by Ellis et al in 2009 Regime ECF-Taxotere compared with ECF – CMF, outcome of TNBC and non TNBC patients has effected and the results of this study comparable with our result.\(^3\) In another study by Cheang MC et al., CMF regimen was more useful than anthracycline-containing regimens in basal-like breast cancer subtype.\(^6\) In our study TNBC was analyzed and subtype of BCLC was not analyzed separately. In a study conducted by Dr. Trere et al. (2009), the prevalence of TNBC was 10.2% among 518 patients and 145 patients received 6 courses of modified CMF chemotherapy. DFS in TNBC, luminal A and HER-2 positive patients were75%, 46% and 50%, respectively. Loss of pRb, the main factor that predicts the response to chemotherapy, was 37.7% in TNBC and 2.3% in non-TNBC patients. pRb is sensitive to DNA damage and drug effects in thymidylate synthetase such as 5-Fu amd MTX. DFS in patients with loss pRb during the 109-month follow-up period was 100%, while it was reported 50 % in other groups.

Moreover, p53 positive, grade III and Ki67>20 were seen in 58.5%, 77.4% and 83% of TNBC patients. The results of the study comparable with our study.\(^2\)\(^,\)\(^7\)

**CONCLUSION**

The results of this study reveals revealed that adjuvant chemotherapy regimen (CMF) after standard anthracycline / taxane–based chemotherapy had no effects in short-term follow-up. Like the previous studies, positive LN, and tumors with high mitotic rates were seen in TNBC patients.\(^8\) To achieve better results, further studies with larger sample size and long-term follow-up are recommended.

**REFERENCES**

1. Yutaka, Yamamoto, et al. Clinicopathological features and Treatment strategy for Triple Negative breast Cancer. Int. J clin on col 2010; 154: 342- 349.

2. Dr. Trere, E. Brighenti, G. Donati. High prevalence of retinoblastoma protein Loss in triple negative breast cancers and its association with a good prognosis in patients treated with adjuvant chemotherapy. Anals on oncology 2009; 1-2.

3. Ellisp, Barrett- Leep , Johnson L et al . Sequential docetaxel as adjuvant chemotherapy for early Breast Cancer an open label, phase III, randomized Controlled trial. Lancet2009; 373: 1681- 1692.

4. - Schneider BP, Winer EP et al. Triple Negative Breast Cancer, Risk factor to potential targets. Clin Cancer Res 2008; 14: 8010– 8018.

5. Di Leo A,Isola J,piette F,et al.A meta –analysis of phase III Trial evaluting the predictive value of HER2 and topoisomerase II alpaha in early breast cancer patients treated with CMF or Antracycline Based adjuvants therapy. Cancer Res 2009; 69: abstract 705.

6. Cheang Mc, Voduc D, Bajdik C et al. Basal – Like breast cancer defined by five biomarkers has
superior prognostic Value than triple Negative phenotype. clin cancer Res 2008; 14: 1368 – 1376.

7. Rakha EA, EI – Sayed ME, Green AR et al. Prognostic markers in triple – negative breast cancer. Cancer 2007; 109: 25- 32.

8. Schneider BP, Winer EP et al. Triple Negative Breast Cancer, Risk factor to potential targets. Clin Cancer Res 2008; 14: 8010– 8018.