Relationship About KI67 and Chemotherapy Regimens About Progression Free Survival in Triple Negative Breast Cancer

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ABSTRACT

Objective: To determine the experience in a public institution (Hospital General de México) the relationship of KI67% and chemotherapy regimens about the progression free survival.

Design: It is a retrospective study in which a total of 64 patients with a 36-month follow-up were evaluated, evaluating the percentage of KI67 and the chemotherapy regimens, which were AC+TXL vs CBP/TXL+AC.

Results: A progression-free survival of 11.9 months was demonstrated in the patients who started with the CBP / TXL-based chemotherapy regimen and sequentially AC versus the 9.7 months achieved with the conventional ACX4 scheme and later add Carboplatin and Paclitaxel, and a Overall in both arms of 10.8 months, the patients who demonstrated the presence of a higher KI67 demonstrated increased progression-free survival compared to those with a low KI67, and with an unexpected surrogate that despite being few patients, those who showed higher levels of Progesterone had a lower survival compared to percentages of 5% or negative.

Conclusions: Despite the fact that the first-line scheme for triple negative breast cancer was sequential and that the sample was only 64 patients, it was shown that adding carboplatin in the first line together with Paclitaxel in patients with high KI67 and without or with a minimal percentage of progresterone receptors increases Progression Free Survival.

Keywords:

Malignancy, Breast Cancer, Triple Negative Breast Cancer (TNBC), Tumors

Introduction

Breast cancer is the most frequently diagnosed malignancy and the main cause of cancer-related death in women. Globally, approximately 2.1 million new female breast cancer cases and 627,000 deaths were estimated to have occurred in 2018 [1]. Recurrence and metastasis are the major cause of these deaths. Approximately 15%-20% of these patients could be classified as "triple-negative." The diagnosis is made by observing exclusion of the expression and/or amplification of three biomarkers (estrogen receptor [ER], progesterone receptor [PR], and

Human Epidermal Growth Factor Receptor 2 [HER2] protein [2].

So-called Triple Negative Breast Cancer (TNBC) is more commonly diagnosed in women younger than 40 years compared to hormone-positive breast cancer [3]. The histology is usually high grade and most commonly interpreted as infiltrating ductal carcinoma, which exhibits geographic necrosis, a pushing border of invasion, and a stromal lymphocytic response. Clinically, TNBC tends to act more violently than other types of breast cancer and is characterized by a high risk of relapse, short progression-free survival (PFS), and overall survival (OS) [4]. One-half of patients with early-stage TNBC (stages I to III) experience disease recurrence, and 37% of patients experience a 5-year mortality rate after surgery [5].

Also, patients with metastatic TNBC have short PFS after failure of first-line chemotherapy (median PFS, 3 to 4 months), suggesting the highly unmet need for the development of a drug targeting TNBC [6]. TNBC is clinically heterogeneous, with deviations in morphology, mutational phenotype, and signaling profiles between tumors. Notably, the diagnostic criteria have not been developed to distinguish a distinct biologic subtype of breast cancer-a "triple-negative" phenotype. A histologic subtype, medullary carcinoma, despite generally being triple-negative, has a very good prognosis [7]. Due to next-generation sequencing, our understanding of the heterogeneity of TNBC is evolving. For example, TNBC can be clustered into at least six subtypes on the basis of gene ontologies and expression profiling: basal-like 1, basal-like 2, immune modulator, mesenchymal, mesenchymal stem–like, and luminal androgen receptor [8]. Additional subtypes include claudin-low and interferon-rich subtypes [9,10]. Furthermore, the tumor suppressor gene p53 (TP53) and several DNA repair genes, particularly the BRCA genes, are either mutated or abnormally expressed in TNBC. These molecular characteristics may influence chemotherapy sensitivity to direct DNA-damaging agents such as platinum [11,12]

Triple-negative breast cancers encompass other molecular subtypes of breast cancer. These include the so-called claudin-low tumors, which are reported to be enriched with cells that have properties similar to those of stem cells and to have features of epithelial-to-mesenchymal transition; the interferon-rich subgroup, which encompasses tumors with a considerably better prognosis than that associated with other triple-negative breast cancers; and the normal-breast–like subgroup, which may be an artifact (i.e., it may comprise samples enriched with a disproportionately high content of stromal and normal cells) [13,14]. Similarly, 18 to 40% of basal-like cancers do not have a triple-negative phenotype on immunohistochemical analysis [15]. Up to 20% of basal-like cancers express ER or overexpress HER2. At the genetic level, triple-negative and basal-like cancers are remarkably heterogeneous.

Amplification of numerous genetic regions has been documented, but the prevalence of each of these amplified regions is low [16]. Triple-negative and basal-like tumors account for about 15% of all invasive breast cancers, and they usually have a high histologic grade. [12,17] Both triple-negative [18] and basal-like [19] breast cancer occur more frequently in young black and Hispanic women than in young women of other racial or ethnic groups. BRCA1 is an important breast-cancer susceptibility gene; more than 75% of tumors arising in women carrying a mutation in this gene have a triple-negative phenotype, a basal-like phenotype, or both [12,17].

KI-67 is a nuclear protein. Cytoplasmic staining and occasional membrane staining of KI-67 can occur with MIB1 antibody and should be ignored when scoring KI-67. Only nuclear staining (plus mitotic figures stained with KI-67) should be incorporated into the KI-67 score that is defined as the percentage of positively stained cells among the total number of malignant cells scored. Similar to other IHC stains, internal positive controls, such as mitotic figures, normal ducts, and lymphocytes, and endothelial and stromal cells (lesser extent), are helpful [20,21].

KI-67 may predict the pathological remission rate in breast cancer patients following neoadjuvant chemotherapy, as an increased KI67 level following neoadjuvant chemotherapy indicates a poor prognosis [22,23]. Therefore, KI67 is considered to be one of the most significant indicators in detecting the proliferation of tumor cells [24]. The expression of KI67 reliably and quickly reflects the proliferation of malignant cells; it closely correlates with the prediction of the development, metastasis and local recurrence of a variety of malignant tumors [25].

Discussion

The study of the 64 patients evaluated during 36 months of follow-up was carried out, where the average progression-free survival of both arms was 10.8 months close to the literature, being higher for the group which started the treatment based on Carboplatin/Paclitaxel and sequentially ACX4 where up to 11.9 months free of progression was obtained compared to the usual scheme of starting with Anthracyclines and without adding Platinums with a survival of 9.7 months (Figure1-4).

The relationship between the schemes and the expression of the percentage of KI67 was significant given that in patients with a KI67 of 100% they had the best progression-free survival, as well as the range of 86 to 100% and, on the other hand, Although there were very few patients due to the type of population being treated, those that expressed progesterone receptors
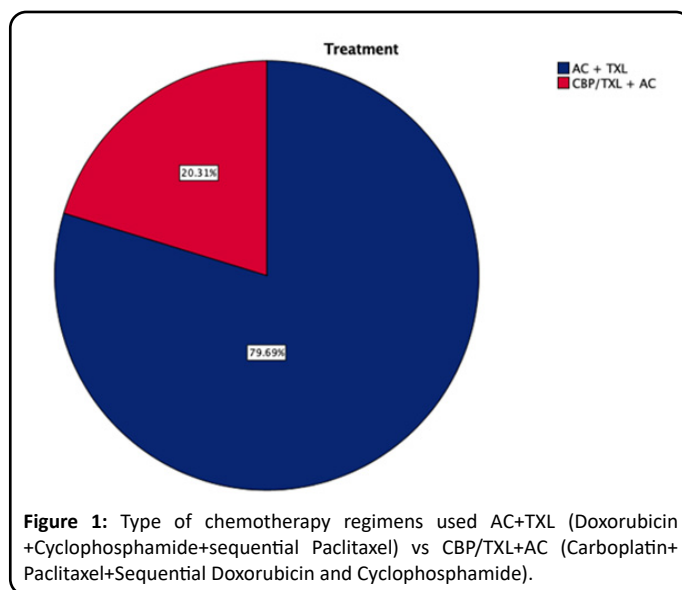

Figure 1: Type of chemotherapy regimens used AC+TXL (Doxorubicin+Cyclophosphamide+sequential Paclitaxel) vs CBP/TXL+AC (Carboplatin+Paclitaxel+Sequential Doxorubicin and Cyclophosphamide).

for the least (5%) had a worse progression-free survival than the pure triple negatives in which there is no expression of hormonal receptors, making an important distinction that the few patients who came to express progesterone receptors of 15% had their median progression-free not exceeding 4 months (Figure5-9).
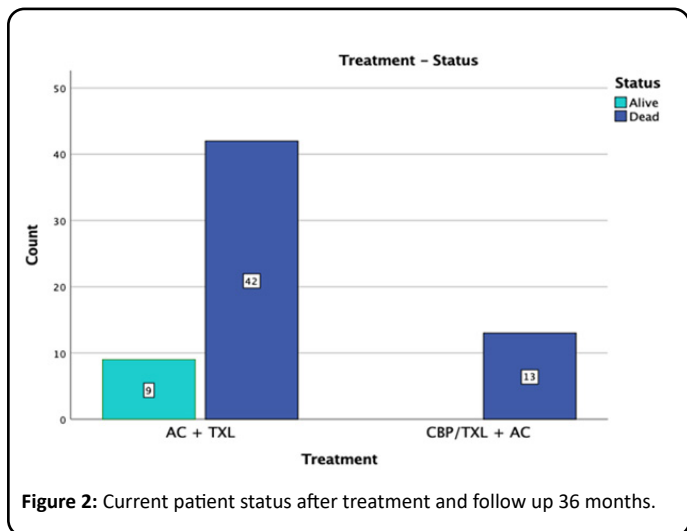

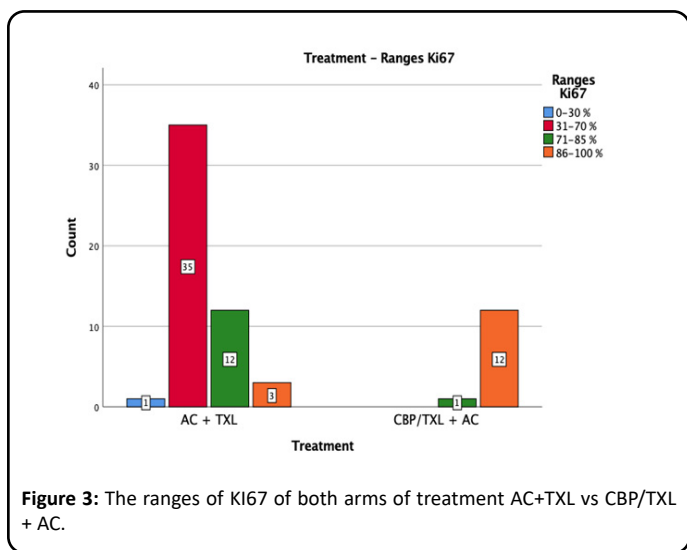**Figure 2:** Current patient status after treatment and follow up 36 months.

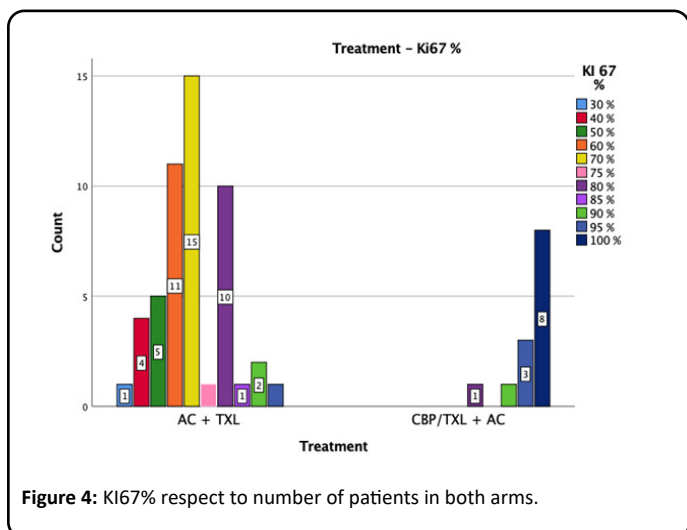**Figure 3:** The ranges of KI67 of both arms of treatment AC+TXL vs CBP/TXL + AC.

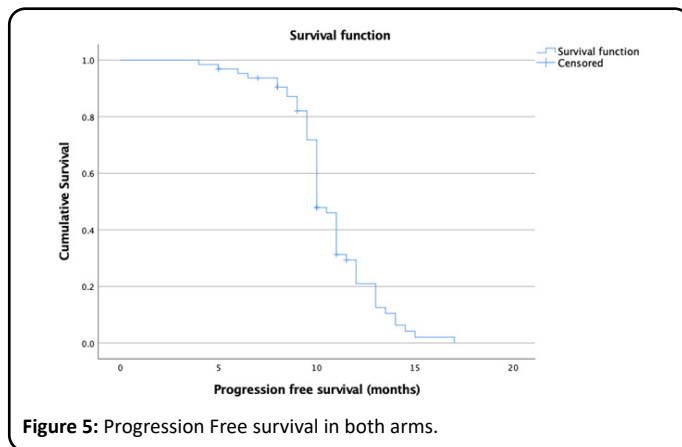**Figure 4:** KI67% respect to number of patients in both arms.

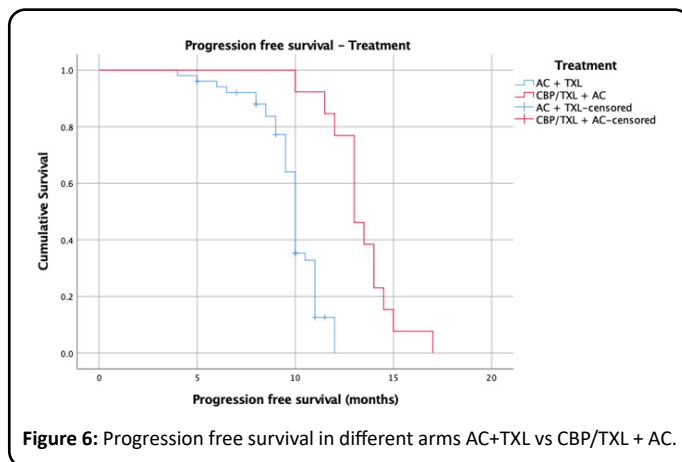**Figure 5:** Progression Free survival in both arms.

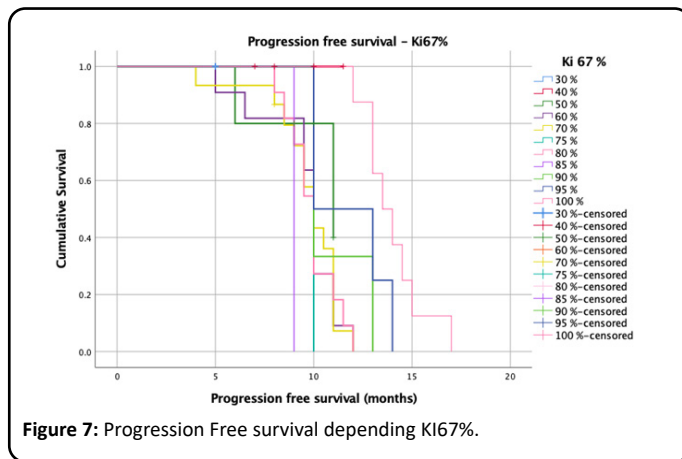**Figure 6:** Progression free survival in different arms AC+TXL vs CBP/TXL + AC.

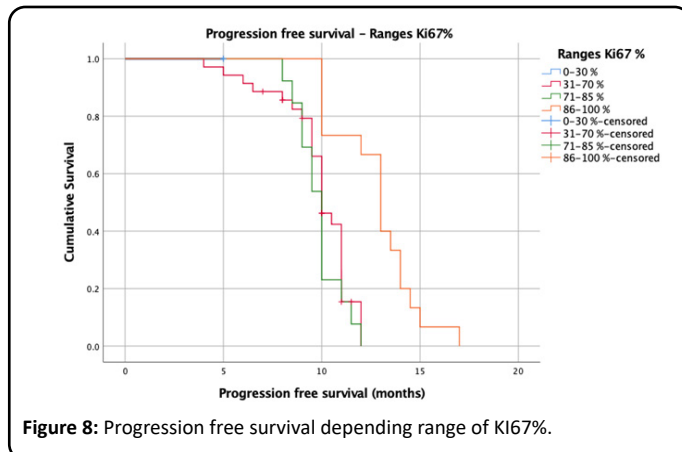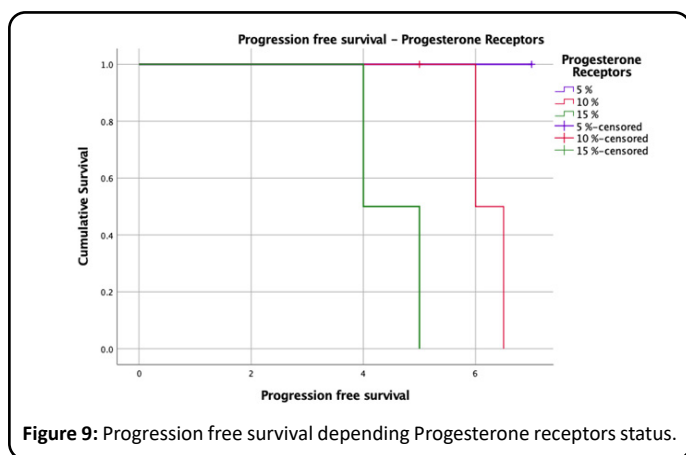

Figure 7: Progression Free survival depending KI67%.

Figure 8: Progression free survival depending range of KI67%.

Figure 9: Progression free survival depending Progesterone receptors status.

Conclusions

It is interesting to know the biology and behavior that triple negative breast cancer can have, both in the response to different chemotherapy treatment schemes that are currently the mainstay that options such as starting with an "inverted therapy" adding an agent such as Platinum we know that there is a decrease in intraluminal pressure added to taxane and subsequently the sequence with anthracyclines or the conventional and accepted worldwide scheme such as the start of Anthracyclines and later Taxanes without adding platinum, which has been shown to increase response rates .

The implication of KI67 was observed that the higher the proliferation rate these tumors have, they will have a greater objective response and in our study, it was demonstrated in progression-free survival with a platinum-based and more "aggressive" scheme where the prolongation in months of 2.2 was observed. months compared to the conventional scheme and a lower KI67.

The fact that they express progesterone receptors gives us a poor prognosis in progression-free survival, as we observed, the vast majority of our patients were a "pure" triple negative with months of survival described in the literature, however the fact that they have expressed estrogen receptors from 5% to 15%, knowing that there are other signaling pathways for expression, these patients had progression-free survival of 4 to 5 months, practically half the months established for the rest of the patients.

References

1. Bray F. Ferlay J. Siegel SI, et al. (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68(1): pp. 394-424.

2. Garrido-Castro AC, Lin NU, Polyak K (2019) Insights into Molecular Classifications of Triple-Negative Breast Cancer: Improving Patient Selection for Treatment. Cancer Discov 9(2): pp. 176-198.

3. Trivers KF, Lund MJ, Porter PL, et al. (2009) The epidemiology of triple-negative breast cancer, including race. Cancer Causes Control 20(7): pp. 1071-1082.

4. Mustacchi G, De Laurentiis M (2015) The role of taxanes in triple-negative breast cancer: literature review. Drug Des Devel Ther 9(1): pp. 4303-4318.

5. Liedtke C, Mazouni C, Hess KR, et al. (2008) Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. J Clin Oncol 26(8): pp. 1275-1281.

6. Thomas ES (2008) Ixabepilone plus capecitabine for metastatic breast cáncer progressing after anthracycline and taxane treatment. J Clin Oncol 26(13): 2223.

7. Livasy CA, Karaca G, Nanda R, et al. (2006) Phenotypic evaluation of the basal-like subtype of invasive breast carcinoma. Mod Pathol 19(2): pp. 264-271.

8. Lehmann BD, Bauer JA, Chen X, et al. (2011) Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J Clin Investig 121(7): pp. 2750-2767.

9. Bertucci F, Finetti P, Cervera N, et al. (2008) How basal are triple-negative breast cancers? Int J Cancer 123(1): pp. 236-240.

10. Turner N, Lambros MB, Horlings HM, et al. (2010) Integrative molecular profiling of triple negative breast cancers identifies amplicon drivers and potential therapeutic targets. Oncogene 29(14): pp. 2013-2023.

11. Reis-Filho JS, Tutt AN (2008) Triple negative tumours: a critical review. Histopathology 52(1): pp. 108-118.

12. FoulkesWD, Metcalfe K, HannaW, et al. (2003) Disruption of the expected positive correlation between breast tumor size and lymph node status in BRCA-1related breast carcinoma. Cancer 98(8): pp. 1569-1577.

13. Collett K, Stefansonn IM, Eide J, et al. (2005) A basal epithelial phenotype is more frequent in interval breast cancers compared with screen detected tumors. Cancer Epidemiol Biomarkers Prev 14(5): pp. 1108-1112.

14. NielsenTO, Hsu FD, Jensen K, et al. (2004) Immunohistochemical and clinical characterization of the basal-like subtype of invasive breast cancer. Clin Cancer Res 10(16): pp. 5367-5374.

15. van de RijnM, Perou CM, Tibshirani R, et al. (2002) Expression of cytokeratins 17 and 5 identifies a group of breast carcinomas with poor clinical outcome. Am J Pathol 161(6): pp. 1991-1996.

16. Abd El-Rehim DM, Pinder SE, Paish CE, et al. (2004) Expression of luminal and basal cytokeratins in human breast carcinoma. J Pathol 203(2): pp. 661-671.

17. Carey LA, Dees EC, Sawyer LR, et al. (2004) The triple negative paradox: primary tumor chemosensitivity of the basal-like breast cancer phenotype. Breast Cancer ResTreat 80(4): pp. 1023.

18. Jones C, Ford E, Gillett C, et al. (2004) Molecular cytogenetic identification of subgroups of grade III invasive ductal breast carcinomas with different clinical outcomes. Clin Cancer Res 10(8): pp. 5988-5997.

19. Abd El-Rehim DM, Ball G, Pinder SE, et al. (2005) Highthroughput protein expression analysis using tissue microarray technology of a large well-characterised series identifies biologically distinct classes of breast cancer confirming recent cDNA expression analyses. Int J Cancer 116(3): pp. 340-350.

20. Suciu C, Muresan A, Cornea R, et al. (2014) Semiautomated evaluation of KI-67 index in invasive ductal carcinoma of the breast. Oncol Lett 7(1): pp. 107-114.

21. Dowsett M, Nielsen TO, A'Hern R, et al. (2011) Assessment of KI67 in breast cancer: recommendations from the international KI67 in Breast Cancer working group. J Natl Cancer Inst 103(22): pp. 1656–64.

22. Yerushalmi R, Woods R, Ravdin PM, et al. (2010) KI67 in breast cancer: prognostic and predictive potential. Lancet Oncol 11(2): pp. 174-183.

23. Masuda H, Masuda N, Kodama Y, et al. (2011) Predictive factors for the effectiveness of neoadjuvant chemotherapy and prognosis in triple-negative breast cancer patients. Cancer Chemother Pharmacol 67(4): pp. 911-917.

24. Zheng JN, Ma TX, Cao JY, et al. (2006) Knockdown of KI-67 by small interfering RNA leads to inhibition of proliferation and induction of apoptosis in human renal carcinoma cells. Life Sci 78(7): pp. 724-729.

25. Selz J, Stevens D, Jouanneau L, et al. (2012) Prognostic value of molecular subtypes, KI67 expression and impact of postmastectomy radiation therapy in breast cancer patients with negative lymph nodes after mastectomy. Int J Radiat Oncol Bio Phys 84(5): pp. 1123-1132.