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RESEARCH ARTICLE

IMPLICATIONS OF NEOADJUVANT CHEMOTHERAPY INTERRUPTION AND SUBSEQUENT SURGICAL DELAY ON THE PATHOLOGICAL RESPONSE IN COVID 19 POSITIVE LOCALLY ADVANCED BREAST CANCER NCI, EGYPT EXPERIENCE

Marwa Mahmoud Selim[1], Dalia Ibraheem[1], AmiraIsmailKhater[3] and Heba Gamal[2]

[1]Department of medical Oncology, National Cancer Institute, Cairo University
[2]Department of surgical Oncology, National Cancer Institute, Cairo University
[3]Department of cancer epidemiology and biostatistics, National Cancer institute, Cairo University

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**Corresponding Author:*
Basim Abdulla

ABSTRACT

Introduction*:** In late December 2019, the first outbreak of COVID 19 appeared in Wuhan, China. The WHO announced the beginning of the pandemic and the COVID 19 as a global health emergency (WHO, 2020). As a result of this serious situation, the health care systems worldwide were overwhelmed by the high number of infected and panic cases resulted in exhaustion of resources. ***Patients and methods: Medical files for breast cancer patients in our institute under neoadjuvant chemotherapy who proved to be infected with COVID 19 virus from the January 2020 till December 2020 were reviewed. ***Results:*** Pathological complete response were seen in 69.0 % of cases (20 patients). Delayed time to CTH either 3weeks or one month didn't affect PCR (P=0.688). However type of surgery had significant relation to PCR. As 10 out of 11 patients (90.9%) who did BCS achieving PCR (P=0.046). ***Conclusion:*** In this study, the interruption of the treatment of the locally advanced breast cancer due to infection by COVID 19 virus had no impact on achieving complete pathological response. The analysis of the temporal delay revealed that the delay from 3 week to one month away from date of next cycle maximum has no impact on pathological response. The type of pathological response may be affected by other clinical and biological factors

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INTRODUCTION

In late December 2019, the first outbreak of COVID 19 appeared in Wuhan, China. The WHO announced the beginning of the pandemic and the COVID 19 as a global health emergency (WHO,2020). As a result of this serious situation, the health care systems worldwide were overwhelmed by the high number of infected and panic cases resulted in exhaustion of resources. And as the virus pandemic was associated with considerable mortality and comorbidities especially in elderly and immuno-compromised persons; different medical societies modified their recommendations and guidelines for the treatment of different diseases in general and cancer in specific to prioritize the treatment of COVID 19 and to postpone the unnecessary interventions. However, this response has its drawbacks especially in cancer patients who delayedtheir active treatment may equal the loss of chance of cure (Desai A, Sachdeva *et al*., 2020). For breast cancer patients, recommendations from international societies like ASCO,ESMO favored postponing surgeries especially in locally advanced cancer patients; the continuation of neoadjuvant treatment even for early cases to increase the social distancing; the need for frequent hospital visits and to meet the need for hospital and ICU beds for COVID patients.(De Azambuja *et al*., 2020),(Curigliano Cardoso *et al*., 2020).

In line with these recommendations, The National Cancer Institute in Cairo, Egypt, minimized the number of elective surgeries for cancer patients and restricted them to emergency and urgent surgeries. Also to hold any active management in COVID19 positive patients and resume it after recovery. As well-known achieving pCR (pathological complete response) following NAT (neoadjuvant chemotherapy) is associated with significantly better EFS and OS, particularly for triple-negative and HER2 (+ve) breast cancer (Cortazar *et al*., 2014). In this study we reviewed and analyzed retrospectively the effect of active treatment delay following covid19 infection in our breast cancer patients in NCI Egypt.

PATIENTS AND METHODS

Medical files for breast cancer patients in our institute under neoadjuvant chemotherapy who proved to be infected with COVID 19 virus from the January 2020 till December 2020 were reviewed. We are following the MOH-Egypt COVID19 protocol for screening and diagnosis. All patients offered routine PCR testing, CT Chest, blood panel analysis including CBC, Ferritin, ESR prior to starting chemotherapy or admission for surgery.

Routine CBC and biochemical testing with monitoring of clinical symptoms like fever or cough were done before each cycle. Data collected included all clinico-pathological features (age, sex, residence, stage, pathological and biological type of the tumor) chemotherapy regimen given and surgery type done and their dates as well as the delay period in treatment due to COVID19 infection. Different clinico-pathological features, chemotherapy received and surgery types were included in the analysis. All the reviewed patients had received our standard NAC protocol. AC (Adriamycin and Indoxan) for 4 cycles followed by 12 weeks of Taxol with Trastuzumab in her2neu positive cases. Delay time wasdefined as the time needed to treat the COVID 19 infection and reestablish the treatment again whether continuation of neoadjuvant chemotherapy or undergoing surgery. It was calculated from first past date of next cycle and reported in days. Patients resuming chemotherapy after being symptoms free for one week at least with normalization of CBC. The delay time in admission was not considered in this study due to the slow-down of all oncological treatment procedures during this year of lockdown of the pandemic. Data management and analysis were performed using Statistical Package for Social Sciences (SPSS) vs. 23. Numerical data were summarized using medians (ranges). Categorical data were summarized as numbers and percentages. Numerical data were explored for normality using Kolmogrov-Smirnov test and Shapiro-Wilk test. Comparisons between the two groups of pathological response regarding the periods (period from diagnosis to surgery and period from end of therapy to surgery) were done using Mann-Whitney test. Chi square or Fisher's tests were used (as appropriate) to compare between the groups with respect to categorical data. All tests were two-sided. P-values < 0.05 were considered significant.

Ethical issues: The institutional review board was contacted and being a retrospective study, it was exempted.

Protection of privacy and confidentiality: This study is a retrospective study that does not impose any risk to the patient, data collection and presentation was anonymous and both privacy and confidentiality were protected to the maximum possibility.

RESULTS

Among One hundred and twenty patients under NAC for breast cancer presented at NCI – Egypt during the period from January 2020 to December 2020. Twenty-nine patients were documented to be COVID19 virus positive with interrupted treatment course. Their age ranged from (30-76) years with a median 53 years. 15 patients (51.7%) were postmenopausal. Comorbidities like hypertension and diabetes represented in 31.0% and 17.2% respectively. Pathological description showed that 12 patients (41.4%) were luminal A, while 4 patients (13.8%) were triple negative. ER was positive in 22 patients (75.9%) and 20 patients (69.0%) were high for KI67%.Delayed time to planned next cycle CTH ranged from 21 to 30 days. After end of treatment course 18patients (62.1%) offered MRM while 11 patients (37.9%) underwent CBS. Time to surgery since date of diagnosis ranging from 7 to 14.1 months with median 9.1 months for those who achieved pathological complete response. Pathological complete response were seen in 69.0 % of cases (20 patients). Delayed time to CTH either 3weeks or one month didn't affect PCR (P=0.688). However type of surgery had significant relation to PCR. As 10 out of 11 patients (90.9%) who did BCS achieving PCR (P=0.046; tables 1, 2 & 3).

Table 1. Pathological response in relation to personal characteristics of COVID-19 locally advanced breast cancer patients (n=29)

Characteristics		Pathological response		P value
		Complete response (CR & RCB-I) (n = 20)	Moderate response (RCB-II & RCB-III)+ poor response (n = 9)	
Menopausal Status	Premenopausal & perimenopausal (n = 14)	9 (64.3)	5 (35.7)	0.700
	Postmenopausal (n =15)	11 (73.3)	4 (26.7)	
Contraception	No (n = 9)	6 (66.7)	3 (33.3)	0.858
	OCP (n = 20)	14 (70.0)	6 (30.0)	
Lactation	No (n = 16)	12 (75.0)	4 (25.0)	0.688
	Yes (n =13)	8 (61.5)	5 (38.5)	
Diabetes	No (n = 24)	17 (70.8)	7 (29.2)	0.633
	Yes (n = 5)	3 (60.0)	2 (40.0)	
Hypertension	No (n = 20)	16 (80.0)	4 (20.0)	0.056
	Yes (n = 9)	4 (44.4)	5 (55.6)	

Table 2. Pathological response in relation to clinico-pathological characteristics of COVID-19 locally advanced breast cancer patients (n=29)

Characteristics		Pathological response		P value
		Complete response (CR & RCB-I) (n = 20)	Moderate response (RCB-II & RCB-III)+ poor response (n = 9)	
ER status	Negative (n = 7)	5 (71.4)	2 (28.6)	1.000
	Positive (n = 22)	15 (68.2)	7 (31.8)	
PR status	Negative (n = 11)	8 (72.7)	3 (27.3)	0.732
	Positive (n = 18)	12 (66.7)	6 (33.3)	
Her2neu status	Negative (n = 16)	9 (56.3)	7 (43.8)	0.130
	Positive (n = 13)	11 (84.6)	2 (15.4)	
KI67 (%)	Low risk (n = 9)	6 (66.7)	3 (33.3)	0.858
	High risk (n = 20)	14 (70.0)	6 (30.0)	
Stage	Whatever T& LN +ve (n = 9)	5 (55.6)	4 (44.4)	0.295
	WhateverT& LN -ve (n = 20)	15 (75.0)	5 (25.0)	
Pathology [a]	IDC GII (n = 18)	12 (66.7)	6 (33.3)	0.363
	IDC GIII (n = 9)	8 (88.9)	1 (11.1)	
Biological profile	Luminal (n = 12)	7 (58.3)	5 (41.7)	[b]
	Her-2-neu enriched (n = 13)	11 (84.6)	2 (15.4)	
	Triple negative (n = 4)	2 (50.0)	2 (50.0)	

Data are presented as number (row percentage). ER: Estrogen receptor, PR: Progesterone receptor, Her2: Human epidermal growth factor receptor 2, IDC: Invasive duct carcinoma, [a] Two cases with Invasive lobular carcinoma were excluded, [b] Test was not done as the assumptions were violated. CR: Complete remission, RCB: Residual cancer burden.

Table 3. Pathological response in relation to management characteristics of COVID-19 locally advanced breast cancer patients (n=29)

Characteristics		Pathological response	
		Complete response (CR & RCB-I)	Moderate response (RCB-II & RCB-III)+ poor response
		(n = 20)	(n = 9)
Treatment protocol	High risk protocol (4AC/4T) (n = 16)	9 (56.2)	7 (43.8)
	High risk protocol (4AC/4T) + herceptin (n = 13)	11 (84.6)	2 (15.4)
Delay time	One month (n = 16)	12 (75.0)	4 (25.0)
	Three weeks (n = 13)	8 (61.5)	5 (38.5)
Type of surgery	BCS (n = 11)	10 (90.9)	1 (9.1)
	MRM (n = 18)	10 (55.6)	8 (44.4)

Data are presented as number (row percentage). CR: Complete remission, RCB: Residual cancer burden. BCS: Breast conservative surgery, MRM: Modified radical mastectomy.

Table 4. Time from end of therapy to surgery (months) in relation to pathologic response (n=29)

	Response grouped		P value
	Complete response (CR & RCB-I)	Moderate response (RCB-II & RCB-III) + poor response	
	(n = 20)	(n = 9)	
	Median (range)		
Period from end of therapy to surgery (months)	1.5 (0.9 - 4.0)	2.0 (1.0 - 5.0)	0.417

Table 5. TN staging in relation to type of surgery (n=29)

		Type of surgery		P value
		BCS	MRM	
		n = 11	n = 18	
T stage	T2 &T3 (n = 15)	5 (45.5)	10 (55.6)	0.597
	T4 (n = 14)	6 (54.5)	8 (44.4)	
N stage	Sentinel LN biopsy (n = 8)	7 (63.6)	1 (5.6)	**0.001**
	Axillary evacuation (n = 21)	4 (36.4)	17 (94.4)	

Data are presented as number (column percentage), T: tumor, N: node, BCS: Breast conservative surgery, MRM: Modified radical mastectomy.

Also cases who underwent sentinel lymph node dissection were 8 patients while those who underwent axillary evacuation were 21 patients with p-value (0.001) and this is comparable to the international studies (Untch *et al*., 2011). Also cases who underwent sentinel lymph node dissection were 8 patients while those who underwent axillary evacuation were 21 patients with p-value (0.001) and this is comparable to the international studies (Untch M, Fasching PA, et al; 2011).

DISCUSSION

In our study we've found that interruption of neoadjuvant treatment course and consequently the delay of surgical procedures of locally advanced breast cancer to treat infection with COVID19 virus has not resulted in adverse pathological outcome. As 69.0% of patient achieved PCR which is comparable to international studies in non covid era (Untch M, Fasching PA, *et al*; 2011). According to the literature the pathological outcome in the form of complete or partial response had been affected mainly by the biological type of the tumor as an independent predictor (Sanford RA, Lei *et al*., 2016). Achievement of pathologic complete response (pCR) in the breast and axilla (ypT0/is ypN0) is relatedto improved survival. This relation has been shown to be greatest in triple-negative breast cancer (TNBC), followed by human epidermal growth factor receptor 2 (HER2)-positive breast cancer (Heil Pfob *et al*., 2020). As the delay in surgery was proved to be a negative predictor of outcome in previous studies that described the effect of delaying screening and surgical treatment imposed by the pandemic especially during the year 2020 (Darai *et al*., 2020). Matching again with what was written in literatures PCR is highly affected with the biology of the tumor especially Her2 status. (Gonzalez-Angulo AM, Litton JK, *et al*; 2009).Although it wasn't significantly related to the biological type in our cohort, complete response was higher in her2 positive type group of patients reaching about 85% (table 2). It reflects value of additional target therapy in candidate patients. Although pathological response was not significantly related to any other clinico-pathological characteristics in our study group, type of surgery done either CBS or MRM was positively related (table 3). Patient underwent CBS in our study experienced higher PCR (P= 0.046). Complete response patients were equally divided between both procedures. This may reflect the clinical burden of tumor residual following NAC. Also could explain the presence of other factors that affects the choice of the type of surgery like the presence of multicentricity, stage T4B/C/D, the patient preference and also the pandemic itself that mandates the least procedure possible to achieve cure as per the recommendations of different societies during the pandemic (Dietz Moran *et al*., 2020). It was recommended that cancer patients infected with COVID 19 virus should delay any elective major surgery after recovery by 8 weeks to decrease the high risk of morbidity and mortality associated with major surgery in association with incomplete resolution of the virus infection(American College of Surgeons , 2020;Vuagnat P, Frelaut M, *et al*; 2020) . None of our patients were infected with the COVID 19 virus after completingtheir chemotherapy regimen, that's why the surgery was not delayed after end of NAC (table 4). Previous study demonstrated a negative effect of the SARS COVID 19 pandemic on the presentation of breast cancer at late stages which had an impact on survival. These studies were addressing the policy of postponing screening and early diagnosis at the beginning of the pandemic (Dai M, Liu D, *et al*; 2020). To the best of our knowledge no studies are available that addresses the effect of interruption of treatment and delay in locally advanced breast cancer patients positively infected with COVID 19 on the pathological response and outcome. This retrospective study is limited by the small sample size and by its retrospective nature but this can be attributed to the number infected during treatment.

Further studies should be done to validate our results and on a large cohort including all the pandemic years and early and locally advanced breast cancer.

CONCLUSION

In this study, the interruption of the treatment of the locally advanced breast cancer due to infection by COVID 19 virus had no impact on achieving complete pathological response. The analysis of the temporal delay revealed that the delay from 3 week to one month away from date of next cycle maximum has no impact on pathological response. The type of pathological response may be affected by other clinical and biological factors.

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