Breast Cancer: Targets and Therapy

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ORIGINAL RESEARCH

Survival and Time to Initiation of Adjuvant Chemotherapy Among Breast Cancer Patients in Uruguay

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Introduction: Increases in disease-free survival and overall survival (OS) with the use of adjuvant chemotherapy in early breast cancer (BC) are widely known; however, the optimal time to initiate treatment with adjuvant chemotherapy remains controversial.

Objective: To evaluate the time elapsed between surgery and the initiation of adjuvant chemotherapy and its possible impact on OS in patients diagnosed with BC stages I–III.

Materials and Methods: This retrospective study included 112 patients diagnosed with BC stages I–III who received adjuvant chemotherapy at the Mastology Unit of the Hospital de Clínicas in Uruguay from 2009 to 2019. OS was estimated using the Kaplan–Meier method, and a Cox proportional hazards model was used to estimate hazard ratios (HRs) and 95% confidence intervals.

Results: No statistically significant association was found between the time from surgery to the initiation of chemotherapy and the described variables. OS was worse for patients initiating chemotherapy more than 90 days after breast surgery (n = 19) (HR 7.63; p = 0.004) and between 61 and 90 days after surgery (n = 46) (HR 4.58; p = 0.040) compared to those who started before 30 days (n = 23). Controlling by type of surgery and stage, the prognosis of patients who started chemotherapy between 61 and 90 days after surgery was similar to that of patients who underwent chemotherapy within the first 30 days, controlling for surgery (HR 4.10; p = 0.056) and controlling for stage (HR 3.76; p = 0.075). Prognosis was worse for patients with stage III disease (p = 0.022) who underwent a mastectomy and/or axillary lymph node dissection (p = 0.025).

Conclusion: Patients who started chemotherapy more than 90 days following surgery and those with stage III disease or underwent mastectomy and/or axillary lymph node dissection who initiated it between 61 and 90 days had a worse OS. Multiple factors are involved in the time between surgery and the initiation of chemotherapy, and further studies are needed to evaluate which of these factors influence the delay of chemotherapy in order to design strategies to avoid such delays and their negative impact on survival.

Keywords: time, adjuvant chemotherapy, breast cancer, survival

Introduction

As observed worldwide, breast cancer (BC) in Uruguay is the most frequent cancer in women and is the leading cause of death from cancer.[1,2] Increases in disease-free survival and overall survival (OS) with the use of adjuvant chemotherapy in early BC have been consistently observed in many patient subgroups.[3] In clinical studies that have evaluated the impact of adjuvant chemotherapy on survival, the time required for enrollment between surgery and the initiation of systemic

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treatment has been defined arbitrarily. Retrospective studies have evaluated the impact of this time on survival; some of them did show a positive relationship between a shorter time and OS.[4,5] In this regard, a meta-analysis also showed that for each 4-week delay in the initiation of adjuvant chemotherapy, there was a 6% increase in the risk of death.[6] However, there is evidence that the magnitude of this impact may differ according to BC subtype.[7] Other studies did not show any relationship between the time interval before chemotherapy initiation and OS;[8–10] although, the number of patients enrolled was low and non-standard (outdated) chemotherapy regimens were administered.

Likewise, there is evidence that punctuality in attendance is associated with better cancer outcomes; therefore, ensuring that adjuvant chemotherapy is provided diligently is an issue that concerns both the medical team and the patients.[11–14] Multiple studies have shown that some sociodemographic factors may contribute to the delay in initiating treatment.[7,15,16]

The primary aim of this study was to evaluate the time elapsed between surgery and the initiation of adjuvant chemotherapy and its possible impact on OS in patients diagnosed with BC stages I–III. We evaluated whether: a) the time elapsed between surgery and the initiation of chemotherapy differed according to variables related to sociodemographic characteristics of the patients (age, marital status, and comorbidities); b) there was an association between the time elapsed between surgery and the initiation of chemotherapy according to variables related to tumor characteristics (stage I–II vs III [tumor, node, and metastasis {TNM} classification, 8th Edition]), biological subtypes, or type of surgery (mastectomy and/or axillary lymph node dissection [ALND]). Survival time was also estimated based upon the time elapsed between surgery and the initiation of chemotherapy.

Methods and Statistical Analysis

This was a retrospective observational study that included patients diagnosed with BC stages I–III who received adjuvant chemotherapy at the Mastology Unit of the Hospital de Clínicas in Montevideo, Uruguay, from 2009 to 2019. Data were extracted from both paper medical records and oncology electronic medical records between December 2019 and May 2020. A descriptive statistical analysis of the population was performed by collecting sociodemographic data, which included the age at diagnosis, place of residence, marital status, social support status, occupation, and education level. Information on comorbidities (overweight/obese, diabetes mellitus, heart failure, ischemic heart disease, hypertension [HT], thyroid dysfunction), tumor size, axillary lymph node status, human epidermal growth factor receptor 2 (HER2) status, estrogen receptor (ER) status, progesterone receptor (PR) status, surgical treatment performed (breast conservative surgery [BCT], mastectomy, ALND, sentinel lymph node biopsy [SLNB], reconstructive surgery), and the type of chemotherapy administered (concurrent anthracyclines and taxanes, sequential anthracyclines and taxanes ± trastuzumab ± hormone therapy, regimen without anthracyclines ± trastuzumab ± hormone therapy) was collected.

Three subtypes of HER2, ER, and PR were defined based on positive or negative tumor expression by immunohistochemistry and fluorescence in situ hybridization, if necessary, for HER2:

1. Hormone receptor+, HER2-: ER+ and PR+, ER-/PR+, ER+/PR-
2. HER2+
3. ER-, PR-, HER2- (triple negative)

The association between the time elapsed between surgery and the initiation of chemotherapy with the variables was evaluated using the chi-square test.

The OS in months was estimated using the Kaplan-Meier method. The differences between survival curves were evaluated using a Log rank test. Simple and multiple Cox models were constructed to evaluate the significance of the hazard ratio using a 95% confidence interval (CI). In all cases, $\alpha = 0.05$, was used. Data analysis was performed using the survival package in R software, version 4.0.2.

The study was conducted in accordance with international ethical standards for biomedical research ("MERCOSUR standards on regulation of clinical studies" and the "Declaration of Helsinki") and with the research regulations approved by the National Ethics Commission in 2019. Patient anonymity was maintained in the analysis of the results, and the study was approved by the Ethics Committee of the Hospital de Clínicas.

Ethical Aspects

The current study was performed in compliance with the international ethical standards applied to biomedical research (ie, the MERCOSUR Standards on the Regulation of Clinical Trials and the World Medical Association's Declaration of Helsinki [including its

amendment dated October 2013]). Patient anonymity was maintained in the analysis, and the study was approved by the research ethics committee of the School of Medicine of the University of the Republic.

Given that it was a retrospective study and an anonymized database was used with biological samples, the ethics committee of the Hospital de Clínicas did not consider it necessary to request the informed consent of the participants.

Results

A total of 112 female patients were included. Most were married or had a partner (49.1%, 55 patients). In terms of occupation, most were housewives (33.9%, 38 patients) or pensioners (28.6%, 32 patients). The remaining sociodemographic data are presented in Table 1.

The median age at diagnosis was 60 years (range, 38–87 years), 71% (n= 80) were stage I–II, and 28% (n= 32) were stage III. Regarding biological subtype, 43% (n= 48) were ER+/PR+/HER2-, 22% were HER2 + (n= 25), and 17% were triple-negative (n= 19), while there was no information regarding the subtype of the remaining 18% (n= 20).

Regarding the number of comorbidities, most of the patients (68.7%, 77 patients) presented with only 1 or no comorbidity and 24.1% (27 patients) between 2 and 4 comorbidities, with no patient having 5 or more comorbidities. It was not possible to collect data in 7.2% (8 patients). The most frequent comorbidities were HT, diabetes mellitus, and being overweight/obese, which were present in 36%, 15%, and 11% of the patients, respectively.

Approximately 50% of patients (n= 56) were treated with conservative surgery, sentinel node biopsy, or axillary nodal biopsy.

The type of surgery performed, systemic treatment administered, and chemotherapy regimens used are shown in Table 2. All patients who were candidates for adjuvant chemotherapy were included. All patients with HER2+ BC received adjuvant trastuzumab, while all patients with hormone receptor positive BC received treatment with adjuvant hormonal therapy.

It was possible to collect the dates of surgery and initiation of chemotherapy treatment in 100 of the 112 patients included. Of these 100 patients, 26% (26 patients) received their first cycle of adjuvant chemotherapy within 30 days, 38% (38 patients) between 31 and 60 days, 16% (16 patients) between 61 and 90 days, and 20% (20 patients) after more than 90 days.

Table 1 Socio-Demographic Characteristics

	n	%
Sex		
Female	112	100
Place of residence		
Montevideo (capital city)	54	48.2
Rest of the Country	58	51.8
Civil status		
Married/common law	55	49.1
Widow	9	8
Single	15	13.4
Divorced/separated	10	8.9
No data	23	20.5
Occupation		
Retired	32	28.6
Housewife	38	33.9
Employee.	17	15.2
Unemployed	6	3
Independent worker	9	8
No data.	10	8.9
Sex		
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Retired	32	28.6
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Employee.	17	15.2
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Independent worker	9	8
No data.	10	8.9

Table 2 Characteristics of the Treatments Received

Type of Adjuvant Systemic Treatment	n	%
Chemotherapy	112	100
Hormonal therapy	81	72.3
Trastuzumab	23	20.5
Type of surgery		
Mastectomy and ALND	47	42
BCT + SLNB	23	20.5
BCT + ALND	33	29.4
Mastectomy + SLNB	6	5.3
Mastectomy + Reconstruction +SLNB	2	1.8
Other	1	0.8
Total	112	100
Chemotherapy regimen		
Sequential anthracycline- and taxane-based regimen	45	40.1
Docetaxel -Cyclophosphamide	27	24.1
Sequential anthracycline- and taxane-based regimen followed by Trastuzumab	15	13.4
Docetaxel, Carboplatin and Trastuzumab	3	2.7
Concurrent anthracycline- and taxane-based regimen	3	2.7
Other	17	15.1
No data	2	1.8
Total	112	100

After analyzing the different variables, no statistically significant association was found between the time elapsed between surgery and the initiation of chemotherapy and age, marital status, number of comorbidities, tumor stage, biological subtype, or type of surgery (Table 3).

It was possible to collect the date of death or last consultation for 88 of the 100 patients for whom the date of initiation of chemotherapy was available and perform the OS analysis stratified according to the time elapsed between surgery and adjuvant chemotherapy with the following categories: less than 30 days, between 31 and 60 days, between 61 and 90 days, or more than 90 days.

With a median follow-up of 47 months (range 27–65 months), the median OS was not reached for those patients who underwent chemotherapy before 60 days. Cox univariate analysis showed a statistically significantly worse OS for the subgroups of patients beginning chemotherapy after 61 and 90 days (HR 4.58; p= 0.04) and more than 90 days (HR 7.63; p= 0.004) versus those beginning chemotherapy before 30 days (Figure 1 and Table 4).

Cox models were adjusted for the time elapsed between surgery and the initiation of chemotherapy and the type of surgery (high morbidity surgery [mastectomy and/or ALND] and stage (I–II vs III).

As can be seen in the data presented in Tables 5 and 6, the risk of death was markedly higher in those who underwent chemotherapy after more than 90 days compared to within the first 30 days after adjusting for the type of surgery (HR 9.1; p= 0.002) and tumor stage (HR 6.48, p= 0.008). A delay of more than 90 days in the initiation of adjuvant chemotherapy was a poor prognostic factor for all patients, even in the multiple models, adjusting for the stage of disease (HR 2.70; p= 0.02) and type of surgery (HR 0.37; p= 0.024).

Discussion

The role of adjuvant chemotherapy in early BC is well established, as it has demonstrated an increase in disease-free survival and OS.[3] Adjuvant chemotherapy, according to its definition, occurs after breast surgery. However, the optimal time to initiate treatment with adjuvant chemotherapy remains controversial in clinical practice. In relation to this, a relevant question to answer is whether a delay in initiation has a negative impact on OS.

Due to the nature of the question, prospective clinical studies are not available to answer this, as they are considered unfeasible and unethical. Several retrospective clinical studies have addressed this question with conflicting results, with some reporting that the time to initiation of chemotherapy affects OS,[4,6,17–20] while others finding no relationship between them.[8–10] We should bear in mind that the studies that found no association between the time to initiation of chemotherapy and OS included a low number of patients and used non-standard treatment regimens.

In our study, it was observed that the time to initiation of chemotherapy after definitive surgery impacts the OS in patients with BC. The results suggest that a delay in the initiation of adjuvant chemotherapy is associated with reduced OS.

Fifty-eight percent of patients underwent adjuvant chemotherapy (65 patients) before 60 days and 74% (83 patients) before 90 days after surgery. Only 16.9% of patients (19 patients) underwent adjuvant chemotherapy more than 90 days after surgery.

Table 3 Chi Square Analysis

Time Between Surgery and Initiation of Chemotherapy						
		Less Than 30 Days	**Between 30–60 Days**	**Between 61–90 Days**	**More Than 90 Days**	**p**
Age	≤60 >60	11 15	21 17	10 6	9 11	0.53
Marital status	Widow, single, divorced Married, free union	6 15	14 14	1 10	9 10	0.07
Number of comorbidities	0–1 ≥2	19 7	28 4	8 8	14 6	0.05
Type of surgery	ALND or mastectomy No ALND or mastectomy	12 14	13 25	8 8	7 13	0.61
Stage	I–II III	20 6	30 8	10 6	12 8	0.34
Biological subtype	TN Her2 like HR+, HER2-	6 4 16	6 9 23	1 13	3 4 10	0.79

With a median follow-up of 47 months, there was evidence that a delay in initiating adjuvant chemotherapy of 61 or more days after surgery, compared to initiating it within 30 days, was associated with a lower OS (HR 4.58; CI 95%, 1.07–19.63; p= 0.004). For patients who underwent chemotherapy between 61 and 90 days and (HR 7.63;

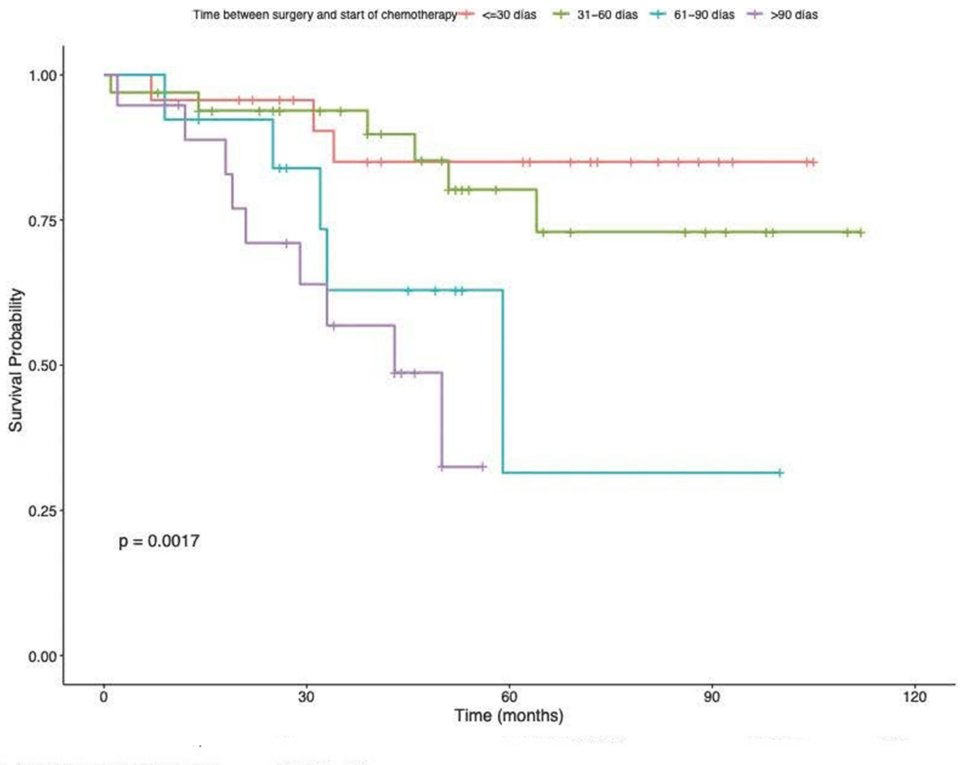

Figure 1 Stratified survival analysis between surgery and start of chemotherapy.

Table 4 Cox Univariate Analysis: Interval Period Between First Surgery and Start of Adjuvant Chemotherapy

Time to Initiation of Chemotherapy After Definitive Surgery	HR	CI 95%	p
≤ 30 days	1		
31–60 days	1.60	0.40–6.43	0.508
61–90 days	4.58	1.07–19.63	0.040
> 90 days	7.63	1.94–30.00	0.004

Table 5 Cox Model Adjusted According to Type of Surgery

		HR	CI 95%	p
Time to initiation of chemotherapy after definitive surgery	≤ 30 days	1		
	31–60 days	1.75	0.44–7.04	0.429
	61–90 days	4.10	0.96–17.47	0.056
	> 90 days	9.10	2.30–36.02	0.002
Type of surgery.	ALND or mastectomy and ALND.	1		
	No ALND neither mastectomy	0.37	0.16–0.88	0.024

95% CI, 1.93–30; p= 0.004) and those who were initiated after 90 days (HR xxx; 95% CI, xx-xx; p= 0.xxx).

In patients treated with less aggressive surgeries, this effect was diminished for the group who underwent chemotherapy > 90 days after surgery; however, a negative impact was maintained in patients with BC stage III, that is, in patients with a higher risk of relapse. This represents a point of vital importance, which, if validated in later studies with a larger number of patients, will help us to select patients who would benefit most from the early initiation of adjuvant chemotherapy and will allow us to design strategies aimed at reducing the time elapsed between surgery and the initiation of chemotherapy.

A delay of more than 90 days in the initiation of adjuvant chemotherapy was a poor prognostic factor for all patients, even when controlling for the stage of disease or type of surgery. These results were consistent with those reported in previous international studies. In this regard, a meta-analysis published by Yu et al, which included 34,097 patients from seven different studies, showed that OS decreased by 15% for each additional 4-week delay in the initiation of adjuvant chemotherapy (HR 1.15; CI 95%, 1.03–1.28).[19]

Several studies have found that a delay in the initiation of chemotherapy may be associated with age, marital status, place of residence, tumor stage, and type of surgery, with the delay being greater in older patients, as well as in those living alone, from rural areas, with BC stage III, and having undergone surgeries with greater morbidity (mastectomy and ALND).[21,22] However, in our study, when analyzing the different variables that could influence the time to the initiation of chemotherapy, no statistically significant association was found for age, marital status, place of residence, number of comorbidities, tumor stage, type of surgery, or biological subtype (Table 3). We must take into account that these values were at the limit of

Table 6 Cox Model Adjusted According to Stage

		HR	CI 95%	p
Time to initiation of chemotherapy after definitive surgery	≤ 30 days	1		
	31–60 days	1.59	0.39–6.39	0.515
	61–90 days	3.76	0.87–16.12	0.075
	> 90 days	6.48	1.64–25.60	0.008
Stage	I–II	1		
	III	2.66	1.15–6.15	0.022

significance for the patients' number of comorbidities and marital status, yet we believe that this should be evaluated in the future with a larger number of patients.

The strengths of the present study include the incorporation of all the patients attended; that is, patients treated in routine clinical practice were represented. In addition, it took into account a significant number of patients, incorporated all age groups, had a prolonged follow-up, and included patients who received chemotherapy regimens appropriate to their risks of relapse following national and international recommendations. Additionally, they were treated with contemporary systemic regimens, and we were able to perform subgroup analysis according to the BC subtype.

The main weakness of this study lies in the impossibility of knowing the determinants of delay in the initiation of chemotherapy. Unfortunately, because of the lack of sufficiently valid data (or data susceptible to appropriate determination), economic characteristics were not investigated in our study, and the same occurred with those related to education level and delays linked to hospital management (late referrals or waiting times for studies). Thus, these aspects would need to be studied in future research. Additionally, our study was limited by its retrospective nature.

Finally, we must emphasize the need for a medical oncologist to inform different physicians managing patients diagnosed with BC (surgeons, imaging specialists, pathologists, etc.) regarding the consequences of delaying the initiation of adjuvant treatment with chemotherapy for the patient. Improving the time to initiation of chemotherapy is a challenge faced by the entire medical team.

Conclusions

In our study, the time between surgery and the initiation of chemotherapy was adequate for most patients, with 80% receiving treatment before 90 days and 63.6% before 60 days. No statistically significant association was found between the time elapsed between surgery and the initiation of chemotherapy based upon age, marital status, place of residence, number of comorbidities, biological subtype, or type of surgery. Patients who initiated chemotherapy more than 90 days following surgery had worse OS. In patients who received chemotherapy between 61 and 90 days, the impact of this time was greater for patients with stage III and those who underwent more aggressive surgeries. These findings suggest that higher risk patients (stage III disease) and patients undergoing mastectomy or ALND experience greater benefits with early initiation of adjuvant chemotherapy in terms of OS.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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