RESEARCH COMMUNICATION

Breast Cancer Pattern and Chemotherapy Response - an Institutional Study in Pakistan

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Abstract

  <u>Background</u>: This study was planned to audit female breast cancers and their chemotherapy in a busy public sector institution. As a case-study, Pakistan provides an opportunity to explore the issue in a low-GDP, low-literacy, populous developing country. <u>Method</u>: Retrospective analysis of the records at Karachi Institute of Radiotherapy and Nuclear Medicine. <u>Results</u>: A total of 3,431 female breast cancer patients presented during 2001-2008, half being <45 years, mostly suffering from infiltrating ductal carcinoma of breast. Further analyzing a subgroup of 183 consecutive patients over six months revealed that only 1.6% were at stage-I, whereas 75% had node-positive disease, including 19.1% with distant metastases. Some 41.6% were either high grade or poorly differentiated. The low grade tumors showed a two-fold likelihood of ER and PR positivity as compared to high grade lesions. 5-Flourouracil, doxorubicin and cyclophosphamide (FAC) constituted the most common chemotherapy. Earlier diagnosis was associated with complete remission. Overall, 33% developed myelotoxicity, more often if age ≥45 years (p=0.012), out of which 60% needed active correction. All those patients who did not experience a drop in total leukocyte count (TLC) below 4×10^9/L did not show complete remission. <u>Conclusions</u>: Infiltrating ductal carcinoma of the breast is the most common type. FAC is the most common chemotherapy. Tendency for late diagnosis, metastatic disease, treatment failure as well as leukopenia especially in ≥45 years is present. Failure to show leukopenia is suggestive of poor therapeutic outcome.

Keywords: Breast cancer - chemotherapy response - asian - leukopenia

Introduction

Breast cancer is the most common malignancy in females worldwide and has shown a global rise in prevalence (Althuis et al., 2005) that is attributable to rising incidence (Remontet et al., 2003). Similarly, carcinoma of breast is the most frequent malignancy among Pakistani females (Hanif et al., 2009; Bhurgri et al., 2006; Azia et al., 2003). Indeed, Pakistan has shown one of the highest frequencies of breast cancer (Bhurgri et al., 2006).

Anticancer chemotherapy is an important treatment modality for breast cancer. Usually FAC regimen comprising of 5-fluorouracil (5FU), doxorubicin (Adriamycin®) and cyclophosphamide is employed as adjuvant, neoadjuvant or palliative chemotherapy. In developed countries, taxanes have largely replaced 5FU (Ahern et al., 2005). Various studies have suggested differences in chemotherapy outcomes as well as severity of adverse effects in different populations (Weinshilboum, 2003; Evans and McLeod, 2003). For example, African-Americans run a greater risk of chemotherapy-induced neutropenia than Caucasians (Hershman et al., 2003; Grann et al., 2008).

To date no account is available regarding the chemotherapy trends and adverse effect profile in Pakistan. As a case-study, Pakistan provides an opportunity to explore the issue in a low-GDP, developing country, where (a) a large proportion of the population lives below the poverty line, thereby limiting the access to health facilities, (b) literacy and health awareness is inadequate, (c) health and education sectors do not get the due attention from the government, and (d) the treatment is planned on the basis of the available data from West, without due consideration of local perspectives. Thus, majority of the population relies on the public sector institutes for cancer treatment.

The port city of Karachi, one of the largest agglomerations in the world, is the largest and most modern city in Pakistan, spread over 3000 square kilometers. It is a provincial capital with a population of more than 18 million. Karachi is often termed 'Mini Pakistan' because all ethnicities are found here. Karachi Institute of Radiotherapy and Nuclear Medicine (KIRAN) is a specialized center in public sector for oncology services that caters a large part of the city. Thus, the institute is a good representation of the problem in local population and its statistics could be safely generalized. This is also supported by Hanif et al., (2009). This study

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was therefore undertaken to audit the pattern of disease, chemotherapy and outcome(s) in a local cohort of breast cancer patients.

Materials and Methods

This cross sectional study was designed at Department of Pharmacology, Ziauddin Medical College, Karachi and conducted at KIRAN. The study was approved from Ziauddin University, Karachi. Percent frequency of breast cancer was calculated according to age groups in all incident cases of breast cancer presenting at KIRAN during 2001-2008.

A smaller cohort of females who presented between October 2007 and March 2008 inclusive, was further analyzed in terms of distribution of pathology, clinical staging at presentation, histological grading, ER, PR and Her2/neu status, chemotherapy details, evidence of myelosuppression and therapeutic response. The data was obtained from the hospital records. The cohort was

Table 1. Patient Characteristics

Parameter		Frequency (Percentage)		
		Adjuvant (n=97)	Neoadjuvant (n=51)	Palliative (n=35)
Diagnosis	Infiltrating ductal carcinoma	93 (95.9)	50 (98.0)	32 (91.4)
	Infiltrating lobular carcinoma	4 (4.1)	-	2 (5.7)
	Others	-	1 (2.0)	1 (2.9)
Side	Right	42 (43.3)	20 (39.2)	23 (65.7)
	Left	55 (56.7)	27 (52.9)	12 (34.3)
	Bilateral	-	4 (7.8)	-
Age Groups	<45 Years	44 (45.4)	24 (47.1)	15 (42.9)
	≥45 Years	53 (54.6)	27 (52.9)	20 (57.1)
Node Positive Disease		56 (57.7)	47 (92.2)	34 (97.1)
Clinical Stage (TNM)	I	3 (3.1)		-
	IIA	2 (2.1)	-	-
	IIB	60 (61.9)	-	-
	IIIA	32 (33)	-	-
	IIIB	-	51 (100)	-
	IV	-	-	35 (100)
Histological Grade (Modified Bloom-Richardson)	I	10 (10.3)	3 (5.9)	-
	II	46 (47.4)	25 (49.0)	8 (22.9)
	III	31 (32.0)	13 (25.5)	6 (17.1)
	Undifferentiated	-	2 (3.9)	5 (14.3)
	Unknown	-	8 (15.7)	16 (45.7)
Her2/neu	Positive	13 (13.4)	17 (33.3)	6 (17.1)
	Negative	23 (23.7)	4 (7.8)	1 (2.9)
	Data not available	61 (62.9)	30 (58.8)	28 (80.0)
Estrogen receptor	Positive	37 (38.1)	24 (47.1)	14 (40.0)
	Negative	51 (52.6)	21 (41.2)	8 (22.9)
	Data not available	9 (9.3)	6 (11.8)	13 (37.1)
Progestin receptor	Positive	36 (37.1)	23 (45.1)	8 (22.9)
	Negative	52 (53.6)	22 (43.1)	14 (40.0)
	Data not available	9 (9.3)	6 (11.8)	13 (37.1)
Radiotherapy	Yes	81 (83.5)	36 (70.6)	23 (65.7)
	No	10 (10.3)	10 (19.6)	10 (28.6)
	Data not available	6 (6.2)	5 (9.8)	2 (5.7)
First line chemotherapy	[a]FAC/FEC	78 (80.4)	39 (76.5)	33 (94.3)
	[b]AC; T	13 (13.4)	8 (15.7)	-
	[c]TAC	3 (3.1)	4 (7.8)	-
	[d]Others	3 (3.1)	-	2 (5.7)

[a]Only three cases received epirubicin instead of doxorubicin; [b]Four cycles of doxorubicin and cyclophosphamide followed by four courses of taxanes; [c]Taxane, doxorubicin and cyclophosphamide given together as six chemotherapy courses; [d]Others: One case each received CMF (cyclophosphamide, methotrexate, 5FU), GEM+TAX (gemcitabine, taxane), MMM (mitomycin, methotrexate, mitoxantrone), GEM+CSP (gemcitabine, cisplatin), high dose AC (doxorubicin, cyclophosphamide).

divided according to the therapeutic intent into adjuvant, neoadjuvant and palliative. The surgical procedure and radiotherapy if any, were recorded. The response to therapy was considered satisfactory, if there was complete disappearance of the lesion and/or no recurrence during follow up as per RECIST guidelines (Therasse et al., 2000). ER, PR, Her2/neu status was assessed according to the immunohistochemistry/FISH kit manufacturer's guidelines (Dako Denmark A/S, ER/PR PharmDx™ and HercepTest™).

Data was entered in SPSS ver 11.0. Percent frequency of various parameters was calculated and presented as tables and graphs. Non-parametric tests, such as Chi square test, Kruskal-Wallis test and Mann-Whitney U test were applied where appropriate.

Results

A total of 3465 breast cancer patients presented at KIRAN during 2001-2008. Out of these, 99% were females. The frequency distribution data (Figure 1) showed that half of the patients were less than 45 years of age (n=1741; 50.25%). The age-group pattern was consistent over the period.

A subgroup of 206 consecutive patients who presented during a period of six months (October 2007 to March 2008) was further analyzed (Figure 2). The age in years ranged from 25 to 71 years with a mode at 40. The patients aged ≥45 years comprised of 53.4% (n=110). One in seven diagnosed patients was younger than 35 years. The 5-year age group distribution suggested a bimodal distribution.

The data of 23 patients (11.2%) was excluded from further analysis because of incomplete staging profile. Table 1. shows that infiltrating ductal carcinoma of breast was the single most common etiology. Out of the remaining 183 cases, only 1.6% were at stage-I, whereas 75% had node positive disease, including 19.1% with distant metastases. Out of 168 cases which could be graded, 41.6% were either high grade or poorly differentiated. Overall, 65% cases had unknown Her2/neu status. Similarly, 15.3% had unknown status for ER and PR.

We divided the subjects according to their histological grading in two groups, a low grade (I & II) and a high grade (III & IV) and compared the age distribution and ER, PR positivity. We found (data not shown) that high grade tumors did not show a predilection for a particular age group. On the other hand, majority (54%) of low grade tumors clustered in age group 35-49 years and closely followed the trend line shown in Figure 2. Additionally, the low grade tumors had almost two-fold likelihood to show positive for ER and PR (data not shown).

In majority the primary chemotherapy consisted of low dose cycles of cyclophosphamide (500mg/m^2) and anthracyclines (50mg/m^2) with either fluorouracil (81.6%) or taxanes (15.6%) irrespective of therapeutic intent. Three out of four patients also received adjuvant radiotherapy.

Table 2 compares the treatment outcomes. Presentation at an early stage of disease was significantly associated with complete remission. Overall, 33% (n=57/172) developed bone marrow suppression, out of which 60%

needed active correction through measures like blood transfusion and/or G-CSF administration. Interestingly, it was observed that all those patients who did not experience a drop in total leukocyte count (TLC) below 4×10^9/L did not show complete remission. The reverse was not true at least partly because of an influence of disease stage at presentation.

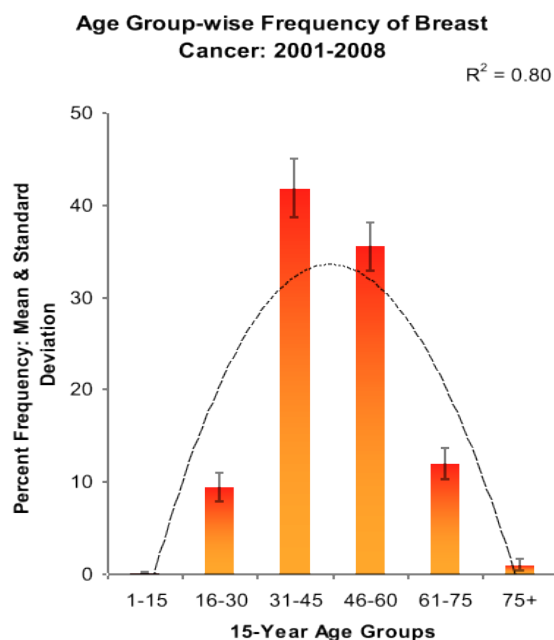Additionally, association of leukopenia, the most common adverse effect, was sought in relation to age

Figure 1. Distribution of Female Breast Cancer Frequency during 2001-2008 in Different Age Groups (n=3431) The value bars show 8-year mean and standard deviation for female breast cancer. The bars represent 0.2±0.2, 9.4±1.5, 41.8±3.2, 35.5±2.6, 12±1.6, 1±0.6 respectively. Trend line is also shown.
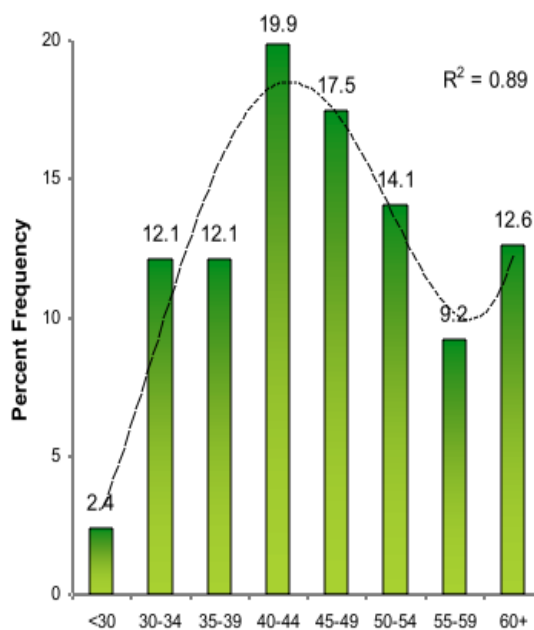

Figure 2. Distribution of Breast Cancer Frequency in Different Age Groups (n=206)

Table 2. Comparison of Treatment Outcomes

Parameters		Frequency (Percentage)		
		Adjuvant (n=97)	Neoadjuvant (n=51)	Palliative (n=35)
Therapeutic Response	[a]Satisfactory	71 (73.2)	27 (52.9)	6 (17.1)
	[b]Unsatisfactory	20 (20.6)	17 (33.3)	24 (68.6)
	Data not available	6 (6.2)	7 (13.7)	5 (14.3)
Progressive Disease		3 (3.1)	2 (3.9)	2 (5.7)
Lost to follow-up		6 (6.2)	9 (17.6)	6 (17.1)
Iatrogenic Bone Marrow Suppression	[c]Needed correction	20 (20.6)	4 (7.8)	10 (28.6)
	[d]Recovered spontaneously	5 (5.2)	2 (3.9)	5 (14.3)
	[e]Minimal or no suppression	69 (71.1)	40 (78.4)	17 (48.6)
	Incomplete record	3 (3.1)	5 (9.8)	3 (8.6)
Needed antimicrobials	Yes	22 (22.7)	4 (7.8)	11 (31.4)
	No	72 (74.2)	42 (82.4)	21 (60.0)
	Incomplete record	3 (3.1)	5 (9.8)	3 (8.6)
TLC at 10th Post-chemotherapy day				
<4 ×10⁹/L	Satisfactory Response	71 (73.2)	27 (52.9)	6 (17.1)
	Unsatisfactory Response	4 (4.1)	2 (3.9)	11 (31.4)
≥4 ×10⁹/L	Satisfactory Response	-	-	-
	Unsatisfactory Response	16 (16.5)	15 (29.4)	13 (37.1)

[a]Satisfactory response was in accordance to the complete response criteria in RECIST guidelines, i.e. complete disappearance of lesions and/or no recurrence; [b]Unsatisfactory included partial or no response according to RECIST; [c]With the help of blood transfusion/ G-CSF to allow timely administration of following chemotherapy dose; [d]To allow timely administration of following chemotherapy dose; [e]No decline in total leukocyte count observed, or there was a decline but it did not fall below 4 ×10⁹/L; [f]p value = 0.006, calculated through Kruskal Wallis Test

(data not shown). The group was divided into (a) younger than 45 or (b) ≥45 to compare treatment outcome and myelotoxicity. Mann-Whitney U Test suggested that the older age group developed myelotoxicity more often than their younger counterparts (p=0.012) but there was no relationship to complete remission rate.

Discussion

The analysis of the data in this study shows a steep upward trend in the breast cancer frequency among women aged 30-44 years. This is in conformity with a large multinational study by Althuis et al (2005). In contrast to their study, an increase with advancing age could not be demonstrated. Rather the trend started to decline at 45 years of age. Figure 2 suggested a bimodal distribution: one in late thirties and early forties, whereas the other one in above sixty. However, the later could not be ascertained due to smaller sample size.

It is noteworthy that a very small number of the patients were diagnosed early (Table 1). A tendency for late diagnosis is implicit in the observation. This is in contrast to a large study from Europe (Blamey et al., 2009) (n=16944, mean age 55 years) in which the majority of breast cancers were diagnosed early as shown by the fact that 66% were lymph node negative. Additionally, they also reported that 29% showed grade-I, 41% grade-II and 30% grade-III pathology. Seventy-five percent were ER positive.

In this study the patients presented with a breast lump with or without discharge from the nipple. Some of the cases presenting with metastatic disease had a long history of slow growing lump in the breast for which the workup was either ignored or deferred by patients due to lack of awareness or low socio-economic status. Others were mismanaged since they sought advice from practitioners of alternative medicine, like homeopaths or traditional herbalists for several months before seeking the expert opinion. This reflects the prevalent poor health administration, and criminal negligence in controlling quackery. Since the country lacks an appropriate media policy, another reason of such a behavior could be unchecked dissemination of hyped claims by these quacks through print media apart from lack of awareness and jeopardized health infrastructure. The situation warrants proper action by the government to prevent further damage.

Before referral to KIRAN, initial management, like diagnostic workup and surgeries were undertaken at other facilities, especially large public sector institutes, where the documentation tended to be incomplete to the extent that 11.2% had insufficient information regarding their staging and hence were excluded from this study. Hence there is a need to standardize the medical record keeping in health facilities. We used only the adequately documented information in this study.

Leukopenia is a manifestation of myelotoxicity. It is a commonly observed serious adverse effect that needs correction either spontaneously or actively, to avoid a delay in administering subsequent chemotherapy cycles.

We observed that the patients older than 45 years are at greater risk of developing leukopenia to chemotherapy as compared to younger. This is in accordance with Muss et al., (2005). Inability to bear the oxidative stress or effectively metabolize various drugs with advancing age could be the underlying mechanism(s). Higher chances of developing iatrogenic leukopenia in older patients draw attention to the need of individualized chemotherapy. Further studies are required in this regard. In this study, reliable data for presence or absence of active correction of the blood counts was available in 172 patients. Out of these, 34 (20%) received either blood transfusion or G-CSF to correct the blood counts to allow timely administration of subsequent chemotherapy cycle. The frequency lies midway between what was reported by Leonard et al., (2003) (n=422, neutropenia 29%) and Vogel et al., (2005) (n=465, neutropenia 11.2%). A suitable prophylactic antimicrobial cover is mandatory in severely leukopenic patients, thus multiplying the treatment cost. We observed that the TLC follow-up has a promising cost-effective prognostic value. It was found that complete lack of a leukopenic response is a bad prognostic sign. It may be hypothesized that the underlying mechanism(s) operating in malignant cells and leukocytes overlap, such as prompt DNA repair and/or efficient handling of oxidative stress or reduced entry into the cells or lesser intracellular retention of drugs possibly due to variability in constitutive expression of efflux transporters. However, this needs further experimental validation. A recent study has suggested that genotypes of drug metabolizing enzymes in this region may differ from other populations (Afsar et al., 2010).

Despite the limitations of this study, such as a retrospective design and limited sample size from a single facility, it is important in terms of prevalent health attitudes and practices, especially because of the large catchment area of this hospital. It also points to the dire need to devise effective health care delivery and management. Establishing research and development (R&D) units, designing appropriate research studies and mandatory provision of R&D funds as part of annual hospital budgets could ultimately improve the patient management. Medical record keeping needs a major uplift. A competent and dedicated manpower is the key element in this regard. With a large number of medical transcriptionists in the country, the task is not beyond reach. Centrally computerized and active medical record could be of value as exemplified by a number of European nations. Since a considerable number lost to follow up, coordination with NADRA (National Database & Registration Authority, Pakistan) could be a way to track down such patients. This model could be applicable to other disciplines also, especially the communicable diseases.

Based on our observations, we recommend running a mass campaign to normalize the health attitude of general public. Emphasis on breast self examination and periodic clinical checkups may contribute in reducing the tendency for late diagnosis thus improving the prognosis on one hand and greatly reducing the management cost on the other, allo wing better allocation of health budget.

Some studies failed to show a 'benefit' from breast self examination as reviewed by Baxter et al (2001). However there are others (Beaulieu, 1998; Nekhlyudov and Fletcher, 2001) who have argued against such notion. Nonetheless, there is a consensus over need for 'sufficient awareness'. A recent article (Khokhar, 2009) from India has shown the paucity of awareness among educated females about breast cancer. With a low female literacy rate in Pakistan the gravity of situation needs no further elaboration.

In conclusion, the most common pathology among breast cancer patients was infiltrating ductal carcinoma. The disease burden was larger in females aged 45 years. Patients mostly presented with advanced disease. FAC was the most common chemotherapy regimen. Iatrogenic leukopenia was more prevalent in females aged 45 years and those with therapeutic failure. Complete remission is in direct proportion to early diagnosis and treatment.

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