Clinical, Histopathological and Molecular Characteristics of Metastatic Breast Cancer in North-Eastern Kazakhstan: a 10 Year Retrospective Study

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Abstract

Background: Breast cancer (BC) is the top cancer among women worldwide and has been the most frequent malignancy among Kazakhstan women over the past few decades. Information on clinical and histopathological features of metastatic breast cancer (MBC), as well as the distribution of molecular subtypes is limited for Kazakh people. Materials and Methods: The present observational retrospective study was carried out at Regional Oncologic Dispensaries in the North-East Region of Kazakhstan (in Semey and Pavlodar cities). Clinical and histopathological data were obtained for a total of 570 MBC patients in the 10 year period from 2004-2013, for whom data on molecular subtype were available for 253. Data from hospital charts were entered into SPSS 20 for analysis by one-way ANOVA analysis of associations of different variables with 1-5 year survival. Pearson correlation and linear regression models were used to examine the relation between parameters with a p-value < 0.05 considered statistically significant. Results: No significant relationships were evident between molecular subtype and survival, site of metastases, stage or ethnicity. Young females below the age of 44 were slightly more likely to have triple negative lesions. While the ductal type greatly predominated, luminal A and B cases had a higher percentage with lobular morphology. Conclusions: In this select group of metastatic breast cancer, no links were noted for survival with molecular subtype, in contrast to much of the literature.

Keywords: Breast cancer- molecular subtypes- mortality- metastasis- North-East Kazakhstan

Introduction

Breast cancer is of great importance throughout Asia (Forman et al., 2014; Ferlay et al., 2015) including Central Asia, the incidence rate for example being recently found to be increasing in Kazakhstan (Bilyalova et al., 2011; Igissinov et al., 2011; 2012; Beysebayev et al., 2015). According to the oncology service of the Kazakhstan for 2013, breast cancer (BC) took first place in the structure of cancer among women, accounting for 11.7% of the total cancers. Reports for neighbouring parts of Russia also emphasize the importance of breast cancer (Podrubnaya et al., 2007; Kutikhin et al., 2012; Dudarev et al., 2013). The situation in Central Asia may be complicated by higher rates in Russians than Turkic inhabitants (Igisinov et al., 2005).

In Kazakhstan the absolute number of new cases in 2012 was 6,252 patients (GLOBOCAN, IARC 2012). Incidence in Kazakhstan amounted to 22.7/100,000. The death rate from breast cancer was 8.1% 000 (after lung cancer and stomach). In general, the incidence and mortality of breast cancer continues to grow steadily in Kazakhstan (Beysebayev et al., 2015). While incidence rates appear to be increasing across the country at around 1.9% per year, and mortality rates are decreasing at 0.8%, there is considerable regional variation within the country.

Survival of breast cancer varies widely depending on a number of factors. Generally the major cause of short survival in breast cancer is formation of metastases (Rezaienzadeh et al., 2012). High mortality in late stages is due to the “incurable” nature of metastatic breast cancer (MBC) at the current time. It is estimated that 6% of patients have metastatic disease at the time of diagnosis and 20% to 50% patients first diagnosed with primary breast cancer will eventually develop metastatic disease. Even with the remarkable advances in research and clinical management, the current treatment strategies for breast cancer metastasis still largely rely on the use of systemic cytotoxic agents, which frequently deteriorate the patient’s life quality due to severe side effects and, in many cases, have limited long-term success.

The prognosis for MBC patients is poor, with

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an estimated 5-year survival of only 26% (Lu et al., 2009). Numerous studies have been done worldwide to estimate survival of breast cancer patients with regard to demographics and clinicopathological features for example shows that tumor characteristics and molecular subtypes of breast cancer metastases significantly influence post-relapse patient survival, emphasizing that molecular investigations at relapse provide prognostic and clinically relevant information. Zaha et al., (2010) demonstrated that molecular differences have been shown to correlate very well with clinical features and survival, even better than traditional histopathological parameters. The discovery of certain molecular characteristics of breast cancers has helped to understand better the pathophysiology of disease and to develop more direct therapeutic strategies. But no such study has been done in Kazakhstan, where there are different ethnic groups.

This study was carried out to find out the impact of age, ethnicity, stage, histological type and molecular subtype dependent on estrogen and progesterone receptor status, and Her 2 neu positivity, on survival of a breast cancer cohort from North East Region of Kazakhstan, registered at the Oncology Department of ROD, Semey and Pavlodar cities. According to the immunohistochemical (IHC) test of ER, PR and HER-2, breast cancer can be divided into 4 different molecular subtypes: Luminal A subtype (ER or PR positive and HER-2 negative), Luminal B subtype (ER or PR positive and HER-2 positive), HER-2 subtype (ER and PR negative, HER -2 positive) and basallike (triple negative) subtype (ER, PR and HER-2 negative) and also important Ki67 overexpression of activity of proliferation of tumour (REF). The present study was to analyze the clinical features of different breast cancer subtypes, and try to find the predictive factors depending on age and other characteristics for patients with metastatic breast cancer.

Materials and Methods

The present study was carried out at Regional Oncologic Dispensary of the North East Region of Kazakhstan (Semey and Pavlodar cities). We selected patients based upon the following criteria: having histologically proven MBC; all types of metastases, stage at the time of registration, no previous or concomitant malignancy.

This observational retrospective study covered a total of 570 patients with histopathologically proven MBC from 2004-2013. Of these, 253 had findings for molecular subtype, clinical and histopathological data, ethnicity and sites of metastasis. were obtained and studied between different age groups in a 10 year retrospective study. For the molecular subtyping, Luminal B (HER2 negative)– ER positive, HER2 negative, and either Ki-67 high or PR low, while Luminal B-like (HER2 positive) – ER positive, HER2 overexpressed or amplified, any Ki-67, and any PR. The cutoff for HER2 of Luminal B was done by Allerd score between 0-8 in which 0-2 is negative, 3-4-intermediate,5-6-positive, 7-8 strong.

Data from hospital charts were entered into SPSS 20 for analysis by one-way ANOVA analysis of associations of different variables, especially molecular subtype and with 1-5 years survival.

Age (years), and the presence or absence of nodal involvement and distant metastasis, 1, 2,3,4,5 year survival was estimated for all patients from the date of diagnosis (date of histopathology verification) to the date of death.

The association of age, stage, molecular subtype (ER, PR, and Her 2 Neu status and Ki67 with molecular subtype was sought employing by ANOVA analysis, also Fisher’s exact test and Tau-Kendall was done to find out percentage of patients for overall survival in relation to molecular subtype. A p-value of less than 0.05 was considered statistically significant.

Results

The total number of cases of MBC analyzed was 570 with molecular subtype data available for 253. Findings
Table 1. Demographic and Tumour Findings for Molecular Subtypes of Breast Cancer, 253 Cases

| Subtypes | Luminal A | Luminal B | Her2- | Luminal B | Her2+ | TN | All | p value |
|----------|-----------|-----------|-------|-----------|-------|----|-----|---------|
| Age Mean (SD) | 57.2 (11.3) | 56.2 (9.7) | 55.1 (8.9) | 51.1 (12.6) | 51.7 (10.0) | 53.2 (10.8) | 0.088 |
| Distribution | 76 | 30 | 42 | 16.6 | 21 | 8.3 | 36 | 14.2 | 79 | 31.2 | 253 | 100 |
| Age group | | | | | | | | | | | | |
| < 44 | 11 | 14.5 | 3 | 7.1 | 7 | 35 | 8 | 22.2 | 21 | 26.6 | 50 | 19.8 |
| 45-59 | 36 | 47.4 | 23 | 54.8 | 11 | 55 | 21 | 58.3 | 39 | 49.4 | 130 | 51.4 |
| ≥60 | 29 | 38.2 | 16 | 38.1 | 2 | 10 | 7 | 19.4 | 19 | 24.1 | 73 | 28.9 |
| Ethnicity | | | | | | | | | | | | |
| Kazakh | 19 | 25 | 17 | 40.5 | 5 | 25 | 14 | 38.9 | 27 | 34.2 | 82 | 32.4 |
| Russian | 50 | 65.8 | 20 | 47.6 | 14 | 70 | 20 | 55.6 | 43 | 54.4 | 147 | 58.1 |
| Other | 7 | 9.2 | 5 | 11.9 | 1 | 5 | 2 | 5.6 | 9 | 11.4 | 24 | 9.5 |
| Stage | | | | | | | | | | | | |
| I-II | 41 | 53.9 | 20 | 47.6 | 10 | 50 | 16 | 44.4 | 45 | 57 | 132 | 52.2 |
| III | 28 | 36.8 | 16 | 38.1 | 8 | 40 | 18 | 50 | 31 | 39.2 | 101 | 39.9 |
| IV | 7 | 9.2 | 6 | 14.3 | 2 | 10 | 2 | 5.6 | 3 | 3.8 | 20 | 7.9 |
| Histologic type | | | | | | | | | | | | |
| Lobular* | 12 | 15.8 | 11 | 26.2 | 4 | 20 | 1 | 2.8 | 6 | 7.6 | 34 | 13.4 |
| Ductal* | 55 | 72.4 | 27 | 64.3 | 15 | 75 | 29 | 80.6 | 58 | 73.4 | 184 | 72.7 |
| Others | 9 | 11.8 | 4 | 9.5 | 1 | 5 | 6 | 16.7 | 15 | 19 | 35 | 13.8 |
| Metastases location | | | | | | | | | | | | |
| Lung | 9 | 11.8 | 4 | 9.5 | 3 | 15 | 2 | 5.6 | 6 | 7.6 | 24 | 9.5 |
| Bone | 21 | 27.6 | 15 | 35.7 | 6 | 30 | 9 | 25 | 20 | 25.3 | 71 | 28.1 |
| Liver | 1 | 1.3 | 4 | 9.5 | 2 | 10 | 3 | 8.3 | 2 | 2.5 | 12 | 4.7 |
| CNS | 4 | 5.3 | 0 | 0 | 1 | 5 | 2 | 5.6 | 7 | 8.9 | 14 | 5.5 |
| Lymph nodes | 25 | 32.9 | 7 | 16.7 | 3 | 15 | 10 | 27.8 | 20 | 25.3 | 65 | 25.7 |
| Pleura | 2 | 2.6 | 2 | 4.8 | 0 | 0 | 0 | 0 | 2 | 2.5 | 6 | 2.4 |
| Skin+scar | 6 | 7.9 | 1 | 2.4 | 0 | 0 | 0 | 0 | 6 | 7.6 | 13 | 5.1 |
| Combined | 8 | 10.5 | 9 | 21.4 | 5 | 25 | 10 | 27.8 | 16 | 20.3 | 48 | 19 |
| Mortality | | | | | | | | | | | | |
| 1 year alive | 64 | 84.2 | 36 | 85.7 | 20 | 100 | 28 | 77.8 | 64 | 81 | 212 | 83.5 | 0.083 |
| dead | 12 | 15.8 | 6 | 14.3 | 0 | 0 | 8 | 22.2 | 15 | 19 | 41 | 16.2 |
| 2 years alive | 56 | 73.7 | 27 | 64.3 | 18 | 90 | 22 | 61.1 | 47 | 59.5 | 170 | 67.2 | 0.06 |
| dead | 20 | 26.3 | 15 | 35.7 | 2 | 10 | 14 | 38.9 | 32 | 40.5 | 83 | 32.8 |
| 3 years alive | 38 | 50 | 15 | 35.7 | 10 | 50 | 17 | 47.2 | 32 | 40.5 | 112 | 44.3 | 0.54 |
| dead | 38 | 50 | 27 | 64.3 | 10 | 50 | 19 | 52.8 | 47 | 59.5 | 141 | 57.7 |
| 4 years alive | 25 | 32.9 | 11 | 26.2 | 7 | 35 | 11 | 30.6 | 21 | 26.6 | 75 | 29.6 | 0.866 |
| dead | 51 | 67.1 | 31 | 73.8 | 13 | 65 | 25 | 69.4 | 58 | 73.4 | 178 | 70.4 |
| 5 years alive | 16 | 21.1 | 7 | 16.7 | 4 | 20 | 6 | 16.7 | 13 | 16.5 | 46 | 18.2 | 0.947 |
| dead | 60 | 78.9 | 35 | 83.3 | 16 | 80 | 30 | 83.3 | 66 | 83.5 | 207 | 81.8 |

*infiltrative

For these are summarized in Table 1 with details for age, stage, histology, ethnicity. Regarding the distribution of molecular subtypes, triple negative (TN) was most common with 31%, followed by luminal A 30%, luminal B 25% and Her2+ 14%.

No significant relationships were evident between molecular subtype and survival (see Figure 1 for Kaplan-Mayer curves regarding time from diagnosis to metastasis, time from metastasis to death and time from diagnosis to death), site of metastases (see Figure 2), stage...
or ethnicity. Main sites were bone and lymph nodes.

Young females below the age of 44 were slightly more likely to have triple negative lesions. While the ductal histopathology greatly predominated in all molecular subtypes, luminal A and B cases had higher percentages with lobular morphology than their TN and Her2+ counterparts.

Discussion

Overview, the present study revealed that in our highly selective population of MBC cases a ductal subtype and late stage were predictive of poor survival at both 1 year and 5 year. Although a number of studies have been done worldwide to estimate survival of cancer patients with regard to demographics and clinicopathological features no such study has been conducted previously in Kazakhstan. Contrary to Europe and America, in Kazakhstan more than 48% of cancer patients present at an advanced stage of the disease.

The lack of any significant influence of molecular subtype is not in agreement with the literature. The distribution of subtypes reflected the relatively low average age, with a greater preponderance of TN/Basal types (see Table 2), even more extreme results being reported by Ihemelandu et al (2007) for young African-Americans.

In the present study there was no statistically significant variation in subtype with the ethnicity, although as expected being Russian was associated with a higher incidence, in line with earlier findings (Igisinov, 2005).

This contrasted with a report that percentage of luminal A type breast cancer in Uygur patients was significantly lower when compared with the Han patients, whereas the percentages of basal-like and Her-2 overexpression types were significantly higher (Guo et al., 2014)

In China, luminal A tumors had the most favorable prognosis, Conversely, HER-2-enriched tumors exhibited the highest rate of locoregional recurrence (Jia et al., 2014)In Indonesia breast cancer molecular subtypes in regard to age, histological grade, lymph node status and staging Her-2+ subtype breast cancer was more commonly diagnosed with large size, positive lymph node metastasis and poor grade (Widodo et al., 2014). Compared with all other subtypes except nonluminal HER2 positive, triple negative tumors had the highest rate of tumor recurrence (p<0.01) (Shim et al., 2014). In Pakistan, triple negative and Her2neu cancers more frequent in younger age group, triple negative cancers being associated with higher grade and proliferation index (Hashmi et al., 2014) Disease free survival rate in the HER-2 positive groups (luminal B and HER-2 enriched) was worse than the HER-2 negative groups (luminal A and triple negative) *+Najafi et al., 2013)Oman, higher stage at presentation (Stage III and IV) was observed in Her2+ tumours (59%), and a

Figure 2. Distribution of Metastases Depending on the Molecular Type

Table 2. Proportions of Various Molecular Subtypes of BC as Reported in Selected Recent Medical Literature

| Study                  | Year | Country          | Luminal A (%) | Luminal B (%) | HER2 (%) | TN/Basal (%) |
|------------------------|------|------------------|---------------|--------------|----------|--------------|
| Ihemelandu et al       | 2007 | USA (African)    | 55            | 12           | 12       | 21           |
| Shibuta et al          | <35  | Japan            | 25            | 14           | 4        | 57           |
| Tamaki et al           | 2013 | Japan            | 71            | 8            | 9        | 12           |
| Wei et al              | <35  | China            | 45            | 17           | 17       | 21           |
| Chuangsawanich et al   | ≥35  | China            | 47            | 16           | 17       | 20           |
| Guo et al              | 2014 | China (Han)      | 38            | 27           | 15       | 20           |
| Hashmi et al           | 2014 | China (Uygur)    | 33            | 20           | 25       | 21           |
| Jia et al              | 2014 | China (Guangzhou)| 41            | 28           | 11       | 21           |
| Song et al             | 2014 | Korea            | 56            | 14           | 14       | 17           |
| Elkalbawy et al        | 2015 | KSA              | 47            | 28           | 7        | 18           |
| Liu et al              | 2015 | China            | 24            | 37           | 18       | 21           |
| Alnegheimish           | 2016 | Saudi Arabia     | 58            | 15           | 12       | 15           |
| Kaplan et al           | 2016 | Turkey           | 33            | 35           | 12       | 20           |
| Zavyalova et al        | 2016 | Russia Tomsk     | 62            | 14           | 15       | 9            |
| Present paper          | 2016 | Kazakhstan       | 30            | 25 (17/8)    | 14       | 31           |

* Unclassified
higher (22.4%) mortality was detected in basal-like/TN tumours +Mehdi et al., 2014a). In Iran, Vascular invasion was more prevalent in HER-2 subtype (Kadiyar et al., 2014).

In Tomsk, various molecular subtypes of breast cancer differ in the morphological structure, the expression characteristics of the primary tumor and the rate of lymphogenous and hemogenous metastasis, luminal.

A very predominant, TN least prevalent, HER2 + most aggressive, largest’ although hemogenous dissemination and N2-3 node status higher in TN (+Zavyalova et al., 2016) Complicated by intratumoral morphological heterogeneity, phenotypic drift Zavyalova et al., 2013, exerts an effect on multidrug resistance (Denisov et al., 2014). Human epidermal growth factor receptor 2-positive and triple negative tumors had a higher histologic grade and a larger tumor size at diagnosis, and they were more common in women under 50 years (Alnegheimish NA, Alshatwi RA, Alhefidi RM, et al. (2016). Molecular subtypes of breast carcinoma in Saudi Arabia. A retrospective study. Saudi Med J, 37, 506-12.

In general, the majority of breast cancers in young women presents with more aggressive tumor biology than in older women (Tichy et al., 2013) but in our study we did not find any statistically significant links between age and stage, or age and histological type.

In Saudi Arabia, luminal A was predominantly found in the old age group, with low tumor grade (p<0.001) and small tumor size, whereas HER-2 and basal-like subtypes were significantly associated with young age, high tumor grade, lymph nodemetastasis and lymphovascular invasion (Elkablawy et al., 2015). In another study, HR- HER2-patients were younger and more obese, compared to HR+ HER2- patients, the other subtype patients having more children and lower frequencies of earlier menarche, later reproductive system in women of Kyrgyzstan.

Regarding site of metastasis, we did not find any significant variation with the molecular subtype, although the high rates for bone and lymph nodes were typical. Earlier differences among subgroups were higher bone incidences (66.2% and 53.9%) in luminal A and B than in HER2-overexpressing (38.9%) and triple negative (45.1%) and the opposite in brain (25.3% in HER2-overexpressing and 23.1% in triple negative vs. 10.1% and 15.1% in luminal A and B) (Kaplan et al., 2016). Breast cancer subtype has been suggested to not be statistically significant predictor of LN positivity, but higher grade and larger tumor size (Liu et al., 2015). Shibuta et al. (2011) and Tamaki et al (2013) found no significant differences between the subtypes regarding age, menopausal status, disease stage, lymphatic invasion, blood vessel invasion and lymph node metastasis, despite links to histological type and grade. The present study showed that survival of metastatic cancer patients was relatively low in Kazakhstan, in future, more emphasis is needed on early detection and screening (Chukmaitov et al., 2008; Besebayev et al., 2015b).

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