Original article

Pathological features and survival outcomes of very young patients with early breast cancer: How much is "very young"?

Giuseppe Cancello [a, *], Patrick Maisonneuve [b], Manuelita Mazza [a], Emilia Montagna [a], Nicole Rotmensz [b], Giuseppe Viale [c, d], Giancarlo Pruneri [c, d], Paolo Veronesi [d, e], Alberto Luini [e], Oreste Gentilini [e], Aron Goldhirsch [a], Marco Colleoni [a]

[a] Division of Medical Senology, Department of Medicine, European Institute of Oncology, Via Ripamonti 435, 20141 Milan, Italy
[b] Division of Epidemiology and Biostatistics, European Institute of Oncology, Milan, Italy
[c] Division of Pathology, European Institute of Oncology, Italy
[d] University of Milan School of Medicine, Milan, Italy
[e] Division of Senology, European Institute of Oncology, Milan, Italy

A B S T R A C T

We collected information on 497 consecutive breast cancer patients aged less than 35 years operated at the European Institute of Oncology. The main aim of the study is to compare biological and clinical features dividing the population by age: <25 years, 25–29 and 30–34 years old. Pattern of recurrence and survival were also analyzed.

Patients aged <25 years had 81.8% poorly differentiated tumors compared with 66.7% and 56.5% in the 25–29 and 30-34 groups, respectively; no other significant difference were found in the distribution of clinical and immunohistochemical features The distribution of Luminal A and B, Triple Negative and HER2 subtypes (immunohistochemically defined) was not statistically different among the three age groups. No difference was found in the incidence of loco-regional relapses, distant metastases, disease-free survival ($p = 0.79$) and overall survival ($p = 0.99$) between the three age groups. This latter findings was confirmed using age as a continuous variable assuming a linear association between age and the outcomes considered, too.

In conclusion, our data indicate that the group of patients with breast cancer below 35 years is essentially a homogenous group when classical clinical and immunohistochemical features were considered.

Introduction

Breast cancer in young age is a topic issue in oncology for many reasons. First, the sharp increase in the number of breast cancers diagnosed in pre-menopausal women reported in several countries over the last years [1,2]. Moreover, the management of breast cancer in young patients (<35 or <40 years) solicits an integrated approach taking into account relevant issues such as fertility preservation and pregnancy.

Some old and historical studies but also more recent analyses used cut-off of 40 years or the cut-off of 35 years to define a woman with breast cancer "young" or "very young". In all these cases they found that young patients (below 35 or 40 years) had a different pattern of recurrence with an increased risk of death and more aggressive clinical and tumor biological characteristics if compared to the older women [3–11].

In a previous recent publication we evaluated biological and clinical features and pattern of recurrence of two groups of young patients (below 35 years and 35–50 aged) with early breast cancer; we analyzed data according to an immunohistochemical classification in four subtypes.

We found that very young patients (below 35 years) with Triple Negative, Luminal B, or HER2-positive breast cancer have a worse prognosis when compared with older patients with similar characteristics of disease [12].

However the choice of a cut-off of age to define a limit for a different clinical and biological behavior may be arbitrary particularly because the biological, hormonal and environmental milieu modeling tumor biology, is continuously modifying during lifetime. Moreover, it is still unclear whether young age as prognostic factor

* Corresponding author. Tel.: +39 02 57489502; fax: +39 02 574829212.
E-mail address: giuseppe.cancello@ieo.it (G. Cancello).

represents a continuous variable or it may be an inherent characteristic of wider subgroups, i.e. premenopausal (less than 50 years) or very young patients (below 35 years) [13–15].

By now we updated our previous information about very young patients with breast cancer and decided to evaluate three subgroups of patients according to three different age ranges, below 25 years, 25–29 years and 30–34 years.

Aim of our study was to analyze biological and clinical features and pattern of recurrence and survival of these three age-groups of very young patients (below 35 years) with early breast cancer.

The reason to select 3 specific age groups can be seen as arbitrary. However the choice to define a priori categorical variables is in general considered easily acceptable by the physicians.

Moreover some previous analyses have already provided results according to age strata (13, 15).

Nonetheless no studies have evaluated both the clinical/biological features and relapse and survival of different strata of very young women with early breast cancer.

Nevertheless we performed an analysis using age as continuous variable to verify and confirm the results about outcome considered, too.

Patients and methods

We extracted information from our prospectively collected institutional database on all consecutive breast cancer patients operated at the European Institute of Oncology (EIO) between January 1995 and December 2006.

Data on the patient's medical history, concurrent diseases, type of surgery, pathological evaluation, and results of staging procedures were available for all patients. Pathological assessment included evaluation of the primary tumor size, histological type and of lymph nodes status including a sentinel node biopsy [16], when applicable. Tumor grade was evaluated according to Elston and Ellis [17] and peritumoral vascular invasion (PVI) was assessed according to Rosen [18]. Estrogen (ER) and progesterone receptor (PgR) status, Ki-67 labeling index (assessed with the MIB 1 monoclonal antibody), and HER2/neu over-expression were evaluated immunohistochemically as previously reported [19]. The threshold for ER and PgR positivity was 1% [18,20,21]. Moreover we used an immunohistochemical classification to define different subtypes of tumors as follows: Luminal A (ER > 0 or PgR > 0) and (Ki-67 < 14%) and (HER2 0/+/++), Luminal B (ER > 0 or PgR > 0) and (Ki-67 ≥ 14%) and/or (HER2 +++), HER2-positive (ER = 0 and PgR = 0) and (HER2 +++), and Triple Negative (ER = 0 and PgR = 0) and (HER2 0/+/++) [12,22,23].

Statistical analysis

The Fisher exact test and the Mantel–Haenszel Chi–Square test for trend were used to assess the association between categorical and ordinal variables, respectively.

The primary endpoints were the incidence of locoregional relapse (LRR), distant metastasis (DM), breast cancer related events (BCE), disease-free survival (DFS) and overall survival (OS). DFS was defined as the length of time from the date of surgery to any relapse (including ipsilateral breast recurrence), the appearance of a second primary cancer (including contralateral breast cancer), or death, whichever occurred first. OS was determined as the time from surgery until the date of death (from any cause) or the date of last follow-up. Cumulative incidence and survival plots according to age were drawn using the Kaplan–Meier method. The log-rank test was used to assess the survival difference between strata.

Table 1
Characteristics of breast cancer patients according to age at diagnosis.

	All patients	Age at diagnosis			P value (trend)
		<25	25–29	30–34	
All	497	22	123	352	
Histology					
Ductal	456	21	118	317	0.46
Lobular	7	0	1	6	
Ductal + lobular	7	0	0	7	
Other	27	1	4	22	
Tumor size					
≤1 cm	58	4	9	45	0.005 (0.06)
1–2 cm	190	6	34	150	
2–4 cm	188	8	64	116	
>4 cm	51	3	14	34	
Unknown	10				
Tumor grade					
G1	33	0	3	30	0.01 (0.0007)
G2	154	3	36	115	
G3	299	18 (81.8%)	82 (66.7%)	199 (56.5%)	
Unknown					
Number of positive nodes					
None	229	9	63	157	0.75 (0.28)
1-3	174	10	41	123	
4-9	51	2	10	39	
10 or more	43	1	9	33	
PVI					
Absent	286	15	71	200	0.59 (0.38)
Present	208	7	51	150	
Unknown	3				
ER					
Absent	126	4	41	81	0.06 (0.36)
Present	371	18	82	271	
PgR					
Absent	175	6	51	118	0.21 (0.65)
Present	322	16	72	234	
CA153					
Absent	268	12	56	20	0.04 (0.06)
Present	152	8	48	96	
Unknown	77				
Ki67					
<14%	48	2	4	42	0.04 (0.02)
14–30%	188	6	47	135	
>30%	260	14 (63.6%)	72 (58.5%)	174 (49.4%)	
Unknown	1				
Her2/Neu					
0/+/++	341	18	78	250	0.15 (0.70)
+++	102	3	32	67	
Unknown	49				
IHC classification					
Luminal A	38	2	3	33	0.06 (0.36)
Luminal B	336	17	80	239	
HER2	29	0	11	18	
Triple negative	94	3	29	62	
Surgery					
Quadrantectomy	345	15	81	249	0.59 (0.44)
Mastectomy	152	7	42	103	

We performed an analysis using age as a continuous variable assuming a linear association between outcomes/endpoints considered and age with a univariate and multivariate analysis.

All analyses were performed with the SAS software, version 8.2 (Cary, NC).

Results

We selected female patients, aged less 35 years (770 patients) presenting with a diagnosis of primary breast cancer.

We excluded patients having had a previous cancer at another site (14 patients), patients receiving neoadjuvant treatment (167 patients), metastatic disease at surgery (20 patients) and presentation with bilateral breast cancer (6 patients).