Comparison of chemotherapy efficacy in metastatic lobular vs. ductal breast cancer (LOBEC)

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Background

Invasive lobular carcinomas (ILC) are thought to be less chemo-sensitive than invasive ductal carcinomas (IDC), as reflected by lower rates of pathological complete response following neoadjuvant therapy. In the metastatic setting, evidence regarding chemotherapy (Cx) efficacy is limited but provides an opportunity for chemotherapy efficacy between the two histological types to be assessed.

Objectives & Methods

PRIMARY ENDPOINT:

Efficacy of chemotherapy in metastatic ILC (mILC) compared with metastatic IDC (mIDC) as measured by time to next treatment –TTNTc (months (m) between start date of first & second chemotherapy regime in all patients (pts) who had at least two lines of chemotherapy)

SECONDARY ENDPOINTS:

Efficacy of endocrine therapy (as measured by TTNT in pts who received first line endocrine therapy and in those that developed endocrine resistance resistance (EnR) as defined by ESMO consensus guideline[1]), time on chemotherapy for each line of therapy (up to 6th line) between mILC and mIDC and overall survival (time from diagnosis metastatic breast cancer to death of last follow-up [OS])

METHODS:

A retrospective review of prospectively collected data for consecutive pts with metastatic ILC (mILC) treated at a single institution between 2000 and 2023 was included. Pts with mILC were matched on a 1:2 ratio with a cohort of pts with metastatic IDC (mIDC) stratified by age (age <60, 60-66 and >66), era of diagnosis (≤2015 and >2015) and initial metastatic burden (≤3 metastatic sites and >3 metastatic sites). Categorisation of histological subtype was derived from pathology report from definitive breast cancer tumour specimen. Tumours were defined as ILC based on microscopic morphology , E-cadherin negativity and without mixed ductal carcinoma cells being present. IDC tumours were E-cadherin positive without a mixed component of lobular invasive carcinoma.

INCLUSION and EXCLUSION CRITERIA:

Key criteria included written pt consent, initial unilateral invasive breast carcinoma meeting definitions for ILC or IDC. Patients with initial discordant bilateral breast cancer (i.e. IDC in one breast and ILC in the other breast) were only included in the ILC cohort if a metastatic biopsy was performed that confirmed the metastatic lesion was ILC. HER2 amplified tumours, any invasive breast cancer histological subtypes other than ILC and IDC, patients with a non-breast cancer malignancy not deemed disease-free were excluded.

Results

- Study population comprised of 376 pts - mILC (122) and mIDC (254) with median age 64y and 62y, respectively.
- A significantly higher proportion of mILC pts had hormone receptor positive/HER2 negative and lower proportion of triple negative disease (p<0.0001).
- Compared to mIDC, mILC pts were more likely to have de novo disease (29% vs. 18%; p=0.02), lower grade tumours (p<0.0001), received endocrine therapy only for metastatic disease (p=0.03) and were less likely to have visceral disease at diagnosis or any time after metastatic diagnosis (20% vs. 45% p<0.0001, 35% vs. 51% <0.0004, respectively; Table 1).
- Median time to commencing chemotherapy from metastatic diagnosis was longer in mILC pts (5.8 v 2.0 m, p=0.03).

Table 1. Patient and tumour characteristics

	IDC	ILC	Fisher's/ Chi²
	254	122	
Age at diagnosis metastatic			
Mean	62 (range 35-90)	64 (range 39-91)	
Stage at Diagnosis			
De novo metastatic	46 (18%)	35 (29%)	0.0195
Recurrence metastatic	208 (82%)	87 (71%)	
Grade			
1	15 (5.9%)	10 (8.2%)	<0.0001
2	102 (40.2%)	93 (76.2%)	
3	118 (46.5%)	11 (9%)	
Unknown	19 (7.5%)	8 (6.6%)	
Histologic Subtype			
Classical		69 (56.6%)	
Pleomorphic		36 (29.5%)	
Unknown		17 (13.9%)	
ER status			
Positive	178 (70.1%)	112 (91.8%)	<0.0001
Negative	75 (29.5%)	8 (6.6%)	
Unknown	1 (0.4%)	2 (1.6%)	
PR status			
Positive	150 (59.1%)	87 (71.3%)	0.0095
Negative	98 (38.6%)	30 (24.6%)	
Unknown	6 (2.3%)	5 (4.1%)	
Molecular subtype			
HR+Her2-	182 (72%)	114 (93.4%)	
Triple negative	69 (27.2%)	8 (6.6%)	<0.0001
Her2+	3 (1.2%)	0	
Metastasis at start of first line therapy			
Bone	84 (33.1%)	55 (45.1%)	
Lung	82 (32.3%)	6 (4.9%)	0.6479
Liver	57 (22.4%)	18 (14.8%)	
Peritoneum, retroperitoneum or intestine	0 (0%)	21 (17.2%)	
Number of metastatic sites at first Mbc			
1	121 (47.6%)	56 (45.9%)	0.5804
2	74 (29.1%)	41 (33.6%)	
≥3	59 (23.2%)	25 (20.5%)	
Number of metastatic sites during Mbc			
1	49 (19.3%)	18 (14.8%)	
2	74 (29.1%)	38 (31.1%)	
≥3	105 (41.3%)	52 (42.6%)	0.0333
Adjuvant treatment (n=295)	208	87	0.18
No adjuvant treatment	23 (11.1%)	9 (10.3%)	
Endocrine only	40 (19.2%)	18 (20.7%)	
Chemotherapy	145 (69.7%)	60 (69.0%)	
Anthracycline ± taxane	118 (81.4%)	55 (91.7%)	<0.0001
Taxane only	16 (11.0%)	3 (5%)	
Other (Non-Anthracycline or Taxane)	11 (7.6%)	2 (3.3%)	

ENDPOINTS:

- There was no significant difference in TTNTc for patients with mILC and mIDC except for those with visceral disease at diagnosis (Table 2, **Figures 1 - 3**).
- There was no significant difference in TTNTc by subtype of mILC (p=0.46) or choice of first line chemotherapy (anthracycline-based p=0.69, taxane only p=0.15, non-anthracycline or taxane p=0.91).
- There was no significant OS difference observed between mILC and mIDC. There was no difference seen in time on each line of chemotherapy up to 6th line except for the 5th line ILC pts, however confidence intervals were wide **(Figure 4).**
- There was no difference in TTNTe (mILC 14.6m vs. mIDC 14.8m, p=0.94). There were no differences in incidence of EnR between the groups. Pts with mILC and primary EnR appeared to have shorter survival (22.6 vs. 33.1 mths, p=0.017). OS was significantly shorter for both histological subtypes in the presence of primary EnR (p<0.0001, Table 2).

Table 2. TTNTc and OS

	IDC	ILC	IDC	ILC	
	No (%)		TTNT median (m)		p value
A. TTNTc (received ≥ 2 lines Cx)					
• All pts	166 (65)	64 (53)	9.1	8.9	0.31
• Visceral disease at diagnosis	78 (31)	14 (12)	9.1	5.5	0.007
B. TTNTe (received first-line endocrine therapy)	102 (40)	65 (53)	14.8	14.6	0.94
			OS median (m)		p value
C. Endocrine resistance	155 (61)	97 (80)			
Primary	30 (19)	14 (14)	33.1	22.6	0.017
Secondary	106 (68)	71 (73)	55.0	47.3	0.10
None	20 (13)	12 (13)	171.0	NR	0.59
OS across categories of resistance within group, p value			<0.0001	<0.0001	
D. OS Total population(n=376)	34.6	36.8			0.98

Primary endocrine resistance was defined as relapse within the first 2 years of adjuvant endocrine therapy or progression within the first 6 months of first-line endocrine therapy for metastatic disease. Secondary endocrine resistance was defined as relapse while on endocrine therapy but after the first 2 years or within 12 months of completing or progression ≥ 6 months after initiating endocrine therapy for metastatic breast cancer while on endocrine therapy.[1]

Figure 1 TTNT based on type of 1st line therapy (months)

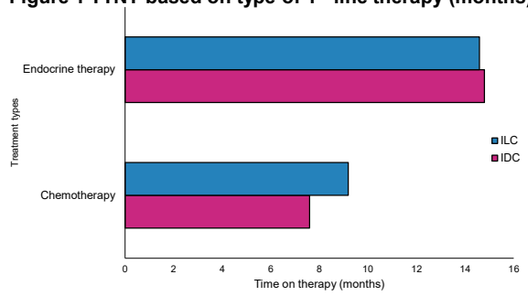
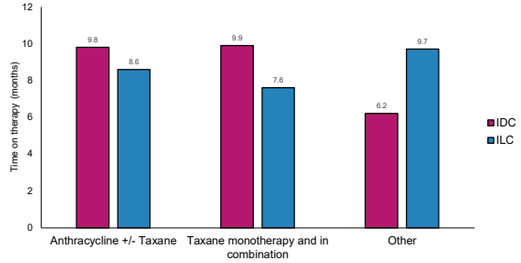


Figure 2 TTNT based on 1st line chemotherapy used (months)



Other chemotherapy includes Capecitabine, CMF, Cisplatin, Gemcitabine and Carboplatin +/- Bevacizumab, Eribulin and Vinorelbine

Figure 3. Time to next chemotherapy regimen

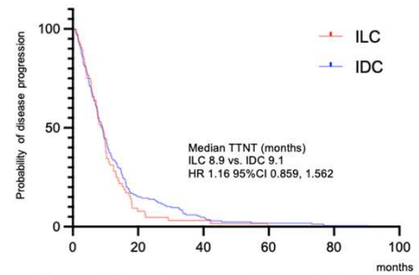
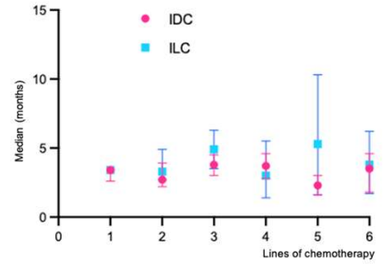


Figure 4. Duration on each line of chemotherapy



Conclusion

- Pts with mILC have a longer time interval to commencing chemotherapy, but efficacy of chemotherapy is similar to pts with mIDC; irrespective of lobular histologic subtype, type of first line chemotherapy regimen used, and sites of metastatic disease, except for those mILC with visceral disease. There was no difference in duration of time on treatment for up to 6 lines of chemotherapy between the 2 groups. There was no significant difference in OS between mILC and mIDC pts treated in this single centre study.
- Efficacy of endocrine treatment when given as first line treatment was similar in both groups with no significant difference when pts were evaluated by presence or absence of endocrine resistance, except for primary EnR, but pt numbers were small in this group.
- Our results demonstrate equivalent chemotherapy efficacy in pts with mILC as compared to mIDC and chemotherapy should be considered at any time during the course of metastatic disease for optimal pt outcome

REFERENCES

1. Cardoso F, Paluch-Shimon S, Senkus E, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). *Ann Oncol*. 2020;31(12):1623-1649