De novo Metastatic Breast Cancer Arising in Young Women: Review of the Current Evidence

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Abstract

Women with metastatic breast cancer remains a heterogeneous group of patients with different prognostic outcomes and therapeutic needs. Young women with *de novo* metastatic breast cancer (dnMBC) represent a peculiar population with respect to tumor biology, prognosis, clinical management and survivorship issues. Overall, these patients are able to attain long-term survival with a proper management of both primary tumor and distant metastases. On the other hand, they are also at higher risk of experiencing a deterioration in their quality of life (QoL) due to primary cancer-related side effects. Young women are also likely to harbor germline pathogenic variants in cancer predisposition genes which could affect treatment decisions and have a direct impact on the lives of patients' relatives. The loco-regional management of the primary tumor represents another thorny subject, as the surgical approach has shown controversial effects on the survival and the QoL of these patients. This review aims to provide an update on these issues to better inform the clinical management of dnMBC in young women.

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Introduction

Although metastatic breast cancer remains an incurable disease, its prognosis can be widely heterogeneous, with overall survival (OS) ranging from less than 2 years to more than 5 years, depending on several prognostic factors.[1]

Young age (Ie. ≤40 years at diagnosis) and *de novo* presentation of breast cancer metastases have shown to be significant contributors to longer survival in this setting.[1-4] Compared to patients with recurrent metastatic breast cancer (rMBC), patients with *de novo* metastatic breast cancer (dnMBC) have longer survivals regardless of breast cancer subtype and clinical prognostic factors, fostering the hypothesis that *de novo* and recurrent disease are two different biological entities.[1-4]

Likewise, women aged ≤40 years with either hormone receptor-positive (HR+) or HER2-positive breast cancer show significantly improved survival compared to their elderly counterpart,[1,5-7] while this age-related prognostic effect has not been observed in triple-negative disease.[8] Such observation is in contrast with what has been observed in the early setting, where breast cancer arising in young women has been associated with increased risk of breast cancer recurrence and death,[8,9] with age-related effect being particularly pronounced in HR+ disease.[9] However, to what extent the biological features of breast cancer in young women contribute to prognosis in the metastatic setting is currently unclear.

Until recently, limited data were available on tumor biology and prognosis of young women with dnMBC. As a consequence, no specific therapeutic recommendations exist for this patient population.[10] However, these women may have different clinical needs compared to other subgroups of metastatic breast cancer patients. Young women with dnMBC could more easily attain long-term

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survival with adequate treatment of both metastases and primary tumor compared to their elderly counterparts.[1-3,5,7] On the other hand, young age has been associated with more aggressive tumor biology and a higher incidence of germline pathogenic variants in cancer predisposition genes which could potentially impact treatment decisions.[3,5] Moreover, young patients have specific survivorship needs which should be promptly addressed, including disruption of work/career commitments, sexual functioning, and family planning.[11,12]

This review aims at addressing all these issues by providing an update on the current evidence about the epidemiology, prognosis, biology and management of dnMBC in young women.

Epidemiology

De novo metastatic breast cancer is currently responsible for about 3%-10% of all breast cancer presentations,[1,4] with its incidence remaining constant (if not increasing) despite the widespread of mammography screening.[13,14]

As a consequence of the sharp decrease in rMBC, whose incidence has declined by more than 10% in the last decades, dnMBC has been progressively accounting for a larger proportion of metastatic breast cancer cases[4]. Data from the SEER Seattle-Puget Sound Registry show that in years 1990-1998 dnMBC accounted for only 15% of all metastatic breast cancer cases in the US, while such proportion rose to 30% in years 2005-2010.[4]

It is currently unclear whether young women are either more or less likely to be diagnosed with dnMBC compared to elderly and middle-aged women. It is estimated that dnMBC currently accounts for 1%-7% of all metastatic breast cancer cases in patients aged ≤40 years.[3,15,16] However, this incidence is reported to be higher in low- and middle-income countries[17] and among non-white women in the US.[2,4,18,19]

In addition, the incidence of dnMBC amongst young women has been increasing at a steady rate over the last decades.[16] In the US, the proportion of dnMBC amongst young breast cancer patients rose from about 4% to 7% in years 1970s-2000s.[16] The reason of such increase is unclear. Because trend in diagnosis of dnMBC remained stable in other age groups, it seems unlikely that the increase observed in young women is due to improvements in diagnostic imaging procedures.[16,20] A possible explanation is the lack of effective breast cancer screening in the young population, which could potentially result in more dnMBC diagnoses. This hypothesis seems to be corroborated by 3 large observational studies, reporting higher frequency of dnMBC amongst younger age groups.[5,21,22] However, other studies report dnMBC to be significantly associated with older age, while being much rarer in women ≤40 years.[2,11,19,23] Moreover, data from an American Tumor Registry showed that the mean age of women with rMBC is significantly lower compared with the dnMBC cohort, indicating that rMBC remains the most frequent form of metastatic breast cancer in young patients.[18]

dnMBC in Young Women: Clinical Presentation and Prognosis

Young age has been associated with more aggressive tumor characteristics in both early and metastatic setting.[5,8,9,24-26] In the metastatic setting, young women are significantly more likely to have multiple visceral metastases at presentation.[5] Notwithstanding these poor prognostic characteristics, and contrary to what has been observed in early breast cancer,[8,9] young metastatic patients show significantly improved survival compared to their elderly counterpart[1,5,7] (Table 1). Of note, such prognostic effect has been observed in all categories but triple negative breast cancer (TNBC), whose prognosis remains poor in all age groups.[1,5,25]

On the other hand, most studies have found that *de novo* occurrence of breast cancer metastases represents *per se* a significant contributor to longer survival across all breast cancer subtypes, irrespectively of patients' age[1,3,18,19] (Table 2). Compared with rMBC, dnMBC is also characterized by a more favorable clinical-pathological presentation, with a significantly lower frequency of TNBC, and a lower incidence of central nervous system (CNS) metastases.[1,2,4,5,18,19,22]

Few studies which specifically explore the clinical and prognostic features of young women with dnMBC are available .[3,25] When those women are compared to their older counterpart, young age remains associated with unfavorable clinical characteristics and yet improved survival outcomes. For instance, young women with HR+/HER2-negative dnMBC have shown higher incidence of liver metastases at diagnosis compared to older women, who are more frequently diagnosed with bone-only disease.[25]

On the other hand, when compared with age-matched rMBC patients, young women with dnMBC appears to have more favorable prognostic characteristics. Similarly to what has been observed for older women, visceral and CNS metastases are less frequent in young women diagnosed with dnMBC as compared with those having recurrent disease.[3] Young patients with dnMBC experience also a significantly longer survival than those with rMBC, with the difference remaining significant also for those rMBC patients with late relapses (>5 years).[3]

The reasons behind the observed favorable prognostic impact of young age and *de novo* metastatic presentation is still unclear. The restrospective nature of most of the available evidence represents a major limitation in our understanding of such prognostic differences.

Young women have less comorbidities and could therefore more easily tolerate multiple lines of treatments, resulting in longer disease control. This would explain the lack of age effect in patients with TNBC, for which very limited treatment options have been available beyond the first- and second-line, until recently.[10] On the other hand, the favourable prognostic effect of young age could be the result of treatment selection bias, which makes young women more likely to receive effective and novel treatments. For instance, the ESME observational study showed that chemotherapy and anti-HER2 therapies were less frequently used in older patients, resulting in shorter OS in women >60 years.[1] The prognostic effect of young age may also relate to the specific biological features of breast cancer arising in young women. However, how breast cancer biology could account for opposite age-related prognostic effects in the early and metastatic setting needs to be further investigated.

With respect to *de novo* presentation of breast cancer metastases, an important role might be played by previous exposures to (neo)adjuvant treatments for early disease. Some studies have shown that survival of dnMBC has significantly improved over the

Table 1 Main Results of the Studies Comparing Overall Survival in Patients With Metastatic Breast Cancer According to Age at Diagnosis

Study, year	Patients, N	≤40 Years N, (%)	Time Span, Year	Overall Survival			
				Hazard of Death, MVA	HR (95% CIs)	*P* value	mOS (months)
Deluche, 2020	22,109	NA	2008- 2016	Age (per incremental year)	1.1 (1.01-1.4)	<.001	NA
Dawood, 2010	3,524	NA	1992 - 2007	Age (per incremental year)	1.01 (1.00-1.01)	<.001	NA
Lobbezoo, 2015	815	NA	2007-2009	Age (per incremental year)	1.02 (1.01-1.02)	<.001	NA
Vaz-Luis, 2017	26,538	1,457 (5.5)[a]	2000-2011	≤40 years	1 (reference)[b]		NA
				40-49 years	1.95 (1.38-2.76)[b]	NA	
				50-59 years	3.50 (2.59-4.71)[b]	NA	
				60-69 years	4.85 (3.54-6.68)[b]	NA	
				≥70 years	8.48 (5.85-12.3)[b]	NA	
Ogiya, 2019	6,302	944 (14.9)[a]	2010-2014	<40 years vs. ≥40 years	0.71 (0.64-0.79)	<.001	<40: 45 ≥40: 33
Frank, 2020	14,403	1,077 (7.5)[a]	2008-2014	>60 years	1 (reference)		38.8
				40-60 years	0.84 (0.80-0.88)	<.001	38.4
				<40 years	0.75 (0.69-0.82)		35.6
Zhao, 2020	7,986[c]	8244 (10.3)	2007-2009	≤40 years	1 (reference)		NA
				41-60 years	1.23 (1.06-1.42)	.006	
				>60 years	1.72 (1.48-2.00)	<.001	

CIs = Confidence Intervals; HR = hazard ratio; mOS = median overall survival; MVA = multivariable analysis; NA = not available.
[a] Includes patients <40 years. Patients = 40 years are included in the control group.
[b] Values represent Odds Ratios with 95% CIs of death within 6 months from metastatic breast cancer diagnosis
[c] Includes only dnMBC patients.

years,[4,20] while no apparent increase has been observed for rMBC.[4] Such observation suggests that treatment improvements in early breast cancer may select rMBC patients with a more resistant phenotype. Nevertheless, some studies report worse survival outcomes also in those patients with treatment-naïve rMBC, suggesting that previous treatment exposure might not be the only reason for worse prognosis in recurrent disease.[2,22]

The Biology of Breast Cancer Arising in Young Women

In the early setting, young age is a well-acknowledged risk factor for breast cancer recurrence and death.[8,26-29] For this reason, breast cancer in young women has long been considered a unique biologic entity,[8,26-28,30] although recent studies have shown that such prognostic effect might be due to a different distribution of breast cancer subtypes across age groups, without any evidence of age-specific molecular differences.[24,31] In 2016, Partridge and colleagues demonstrated that the age group ≤40 years was significantly enriched for HER2-positive and TNBC subtypes, largely explaining the worse prognosis observed in the young population.[9] After adjusting for breast cancer subtypes, young age remained a significant contributor for poorer survival only in HR+ breast tumors, while no age-related differences were observed for the other subtypes.[9] In line with these findings, most gene expression studies showed that age-related genomic differences are limited to HR+ breast cancer cases.[27,30] Young women with HR+ breast cancer show higher proportion of *GATA3* mutations, hypermethylation of *ESR1*, and increased activation of *EGFR*, which are hallmarks of increased endocrine resistance.[8,26,30] The identification of five distinct breast cancer molecular subtypes at the PAM50 assay with different biological features, response to treatments and prognosis has put these genomic features in a wider context.[32-34] In fact, PAM50-based breast cancer molecular subtypes, namely Luminal A, Luminal B, HER2-Enriched (HER2-E), Basal-like and Normal-like, have shown to follow a different distribution depending on age, with young women being affected by more Luminal B, HER2-E and Basal-like tumors compared to older women (Figure 1).[24] The skewed distribution towards Luminal B and non-Luminal subtypes in the young age group might account for most of the previously reported genomic differences between young and older patients, suggesting that age *per se* is not associated with distinct molecular alterations. Accordingly, women ≤40 years showed higher proportion of high-risk tumors even when classified by other genomic signatures.[31]

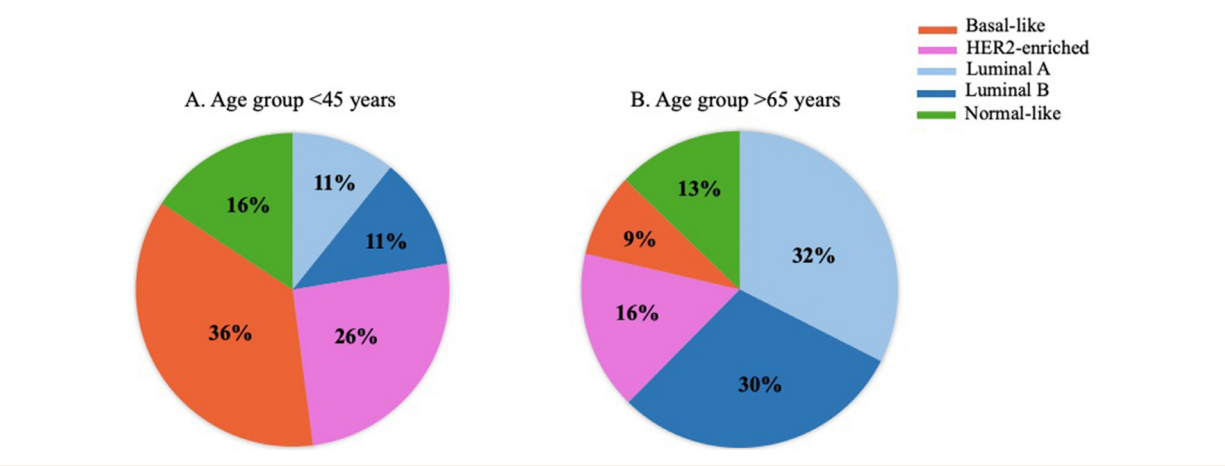
In light of these evidences, it seems counterintuitive that the very same biology contributing to the worse prognosis of young women in the early setting is then associated with longer survival in the metastatic setting. However, very few data are available on the distribution of breast cancer subtypes in metastatic patients according to age groups.[35] Moreover, the PAM50 subtype classifier might not fully capture the biological complexity of breast cancer, and further research is needed to integrate the prognostic role of other classifications which take into account critical molecular features, such as

Table 2 Main Results of the Studies Comparing Overall Survival in Patients With *De Novo* and Recurrent Metastatic Breast Cancer

Study, year	Patients, N	dnMBC N, (%)	rMBC N, (%)	Time Span, Year	Overall Survival			
					Hazard of Death, MVA	HR (95% CIs)	*P* value	mOS (months)
Deluche, 2020	22,109	6,658 (30.1)	15,451 (69.9)	2008- 2016	MFI 6-24 mo vs. dnMBC	2.32 (2.19-2.45)	<.001	NA
					MFI > 24 mo vs. dnMBC	1.14 (1.10- 1.19)	<.001	
Dawood, 2010	3,524	643 (18.2)	2,881 (81.8)	1992 - 2007	rMBC vs. dnMBC	1.75 (1.47 2.08)	<.001	dnMBC 39.2 rMBC 27.2
File, 2020	830	223 (26.9)	607 (73.1)	2011-2017	dnMBC vs. rMBC	0.59 (CIs NA)	<.001	dnMBC 34.0 rMBC 22.0
Frank, 2020	14,403	4,058 (28.2)	10,345 (71.8)	2008-2014	dnMBC vs. MFI > 24 mo	0.84 (0.80-0.89)	<.001	NA
McKenzie, 2020*	932	76 (8.2)	856 (91.8)	2000-2008	rMBC vs. dnMBC	2.67 (1.92-3.71)	<.001	NA
Malmgren, 2018	1,158	247 (21.3)	911 (78.7)	1990-2010	rMBC vs. dnMBC	1.82 (1.53-2.16)	<.001	dnMBC 47.0 rMBC 22.0
Lobbezoo, 2015	815	154 (18.9)	661 (81.1)	2007-2009	MFI < 24 mo vs. dnMBC	1.97 (1.49-2.60)	<.001	dnMBC 29.4 MFI (< 24) 9.1 MFI (>24) 27.9
					MFI > 24 mo vs. dnMBC	0.89 (0.70-1.14)	.358	
Tripathy, 2019**	977	487 (49.8)	490 (50.2)	2012-20	dnMBC vs. rMBC	0.55 (0.44-0.69)	<.001	dnMBC NR rMBC 44.5

CIs = Confidence Intervals; dnMBC = de novo metastatic breast cancer; HR = hazard ratio; MFI = metastasis-free survival; MVA = multivariable analysis; rMBC = recurrent metastatic breast cancer; mOS = median overall survival; mo = months; NA = not available.
*Includes only patients ≤40 years.
**Includes only HER2+ metastatic breast cancer patients.

Figure 1 Distribution of molecular subtypes in early breast cancer patients according to age: age < 45 years (A) and age >65 years (B). Data extracted from Anderson et al. JCO 2011.



PI3KCA mutations,[36] immune infiltration[37,38] and PD-L1 expression.[39,40]

Lastly, it is important to highlight that young and middle-aged patients display a different prevalence of germline pathogenic variants in *BRCA1* and *BRCA2* genes, with *BRCA*-mutant tumors being more frequent in younger patients.[11,41,42] Germline pathogenic variants in *BRCA1* and *BRCA2* genes have been associated with Basal-like and Luminal B subtypes, respectively,[43,44] suggesting that genetic predisposition might partly contribute to the higher incidence of aggressive breast cancer subtypes in young women.[45]

The POSH study currently represents the only observational study reporting *BRCA* mutational status in young patients with metatstatic breast cancer.[3] Interestingly, a much higher prevalence of germline *BRCA1* mutations was found in young women with rMBC (~9%), while the largest proportion of germline *BRCA2* mutations was found in the dnMBC group (~12% vs. 1.3%).[3] This might be the result of the different patterns of metastasization of Basal-like and Luminal tumors; however, further studies are warranted to confirm these intriguing findings.

The Biology of dnMBC

As for breast cancer arising in young women, distant involvement at presentation is thought to represent a peculiar biological entity. Such hypothesis seems to be supported by the observation that, in women ≥ 50 years, the widespread of mammography has generated more localized disease at diagnosis without congruently down staging dnMBC cases,[13,14,46,47] indicating that dnMBC might occur as a systemic disease by the very time it is detectable.[13,14]

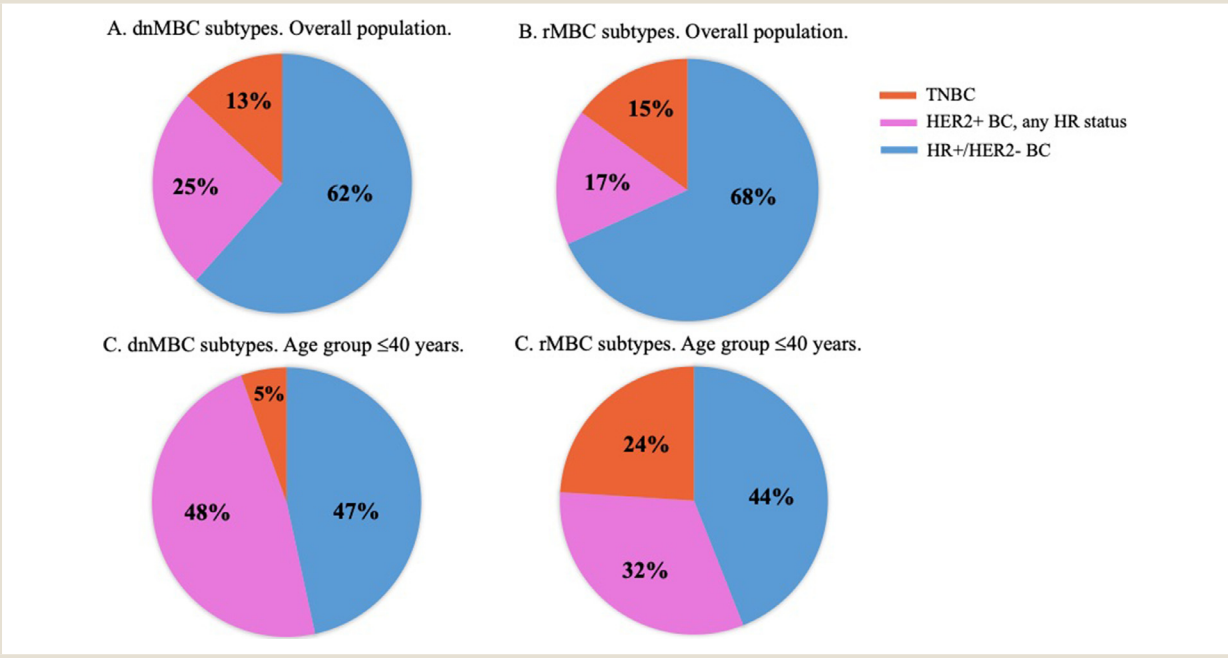
In line with such hypothesis, many observational studies demonstrated significant biological differences between *de novo* and recurrent metastatic breast cancer. In the age group ≤40 years, patients with dnMBC are more likely to be HER2-positive and much less likely to be affected by triple-negative disease as compared with rMBC patients (Figure 2C and Figure. 2D).[3,25]

Similarly, data from the ESME-MBC cohort showed that dnMBC are enriched with HER2-positive tumors and less likely to be HR+/HER2-negative in all age groups (Figure. 2A and Figure. 2B).[1]

From a molecular perspective, recent data from targeted DNA sequencing showed significant genomic differences between primary tumors of patients with dnMBC and those with rMBC, although an analysis according to age groups was not carried out.[48] In any case, within the HR+/HER2-negative subtype, a greater prevalence of alterations in genes involved in epigenetic modulation (Eg. *KMT2D, SETD2, BRD4*), and a higher incidence of *PIK3CA* mutations were found in the dnMBC cohort, while alterations in DNA damage repair genes (*TP53, BRCA1*) were more frequent in rMBC patients. These findings suggest the predominance of the Luminal A phenotype in HR+ dnMBC, with rMBC displaying more aggressive characteristics. In TNBC, a much higher prevalence of *MYB* amplification was found in the *de novo* cohort (21% vs 0%). C-Myb is known to promote invasion through the activation of the beta-catenin pathway, indicating that such alteration may be the biological driver of early metastasization in triple-negative dnMBC.[49] Another *in silico* analysis from the Cancer Genome Atlas (TCGA) showed a significant down-regulation of immune and pro-inflammatory genes in patients with dnMBC compared to those with rMBC, indicating that tumoral immune escape and host immune response might determine the type of metastatic development.[50]

Overall, these data suggest the existence of true biological differences between dnMBC and rMBC, that might be independent from patients' age. Nevertheless, whether these features may have clinical implications is yet to be defined.

Figure 2 Distribution of breast cancer subtypes in the de novo and recurrent metastatic breast cancer: de novo (A) and recurrent (B) metastatic breast cancer in the overall population (data extracted from Deluche et.al EJC 2020); de novo (C) and recurrent (D) metastatic breast cancer in the age group ≤40 years (data extracted from McKenzie et al., BJC 2020); dnMBC = de novo metastatic breast cancer; rMBC = recurrent metastatic breast cancer; TNBC = triple negative breast cancer; BC = breast cancer; HR = hormone receptors.



Challenges in the Management of dnMBC in Young Women

Until recently, young women have been underrepresented in randomized clinical trials (RCT) on MBC, and treatment recommendations for this patient population have been usually extrapolated from the evidence available in older women.[11,51] However, differences in clinical presentation, menopausal status, tumor biology, and specific survivorship needs have undermined the transferability and applicability of such evidence to young patients. As a consequence, young women with metastatic breast cancer have frequently been treated in discordance with international guidelines,[52] with the exception of young women with HER2-positive breast cancer, for whom the use of chemotherapy in association with anti-HER2 blockade appears to be even more frequent than for older women.[1]

This scenario has dramatically changed in the last few years, with results from large clinical trials providing new important data to better inform treatment choices in this population, especially in the case of HR+ and *BRCA*-mutant tumors.

New Therapeutic Options in Young Women With dnMBC: HR+/HER2-Negative Breast Cancer

In HR+/HER2-negative breast cancer, the exclusion of premenopausal patients from clinical trials with endocrine therapy has led to a higher prescription of chemotherapy as upfront treatment.[52] This scenario has partially changed following pivotal trials on first-line treatments with CDK4/6 inhibitors. The disruption of breast cancer cell cycle through the inhibition of CDK4/6 alongside endocrine therapy has shown to improve OS in patients with HR+/HER2-negative metastatic breast cancer, irrespectively of menopausal status.[53-59] The MONALEESA-7 has been the first phase III trial to address such combination as a first-line treatment enrolling exclusively premenopausal patients.[53] This trial randomized 672 premenopausal women to receive either ovarian function suppression (OFS) plus endocrine therapy (tamoxifen or aromatase inhibitor) plus ribociclib or OFS plus endocrine therapy and placebo. A statistically significant and clinically meaningful longer OS in the ribociclib arm was observed (HR: 0.76, 95% Confidence Intervals [CI]: 0.61 - 0.96).[53] About 40% of patients had metastatic disease at presentation, therefore falling in the dnMBC category. Subgroup analyses did not show interaction between type of occurrence of metastases (*de novo* versus recurrent) and treatment efficacy, with the ribociclib arm outperforming endocrine therapy alone across all subgroups. Nevertheless, the benefit of the addition of ribociclib to standard endocrine therapy appears to be particularly pronounced in young women with dnMBC, with almost a 60% reduction in the hazard of progression or death.[53]

Importantly, the Young-PEARL phase II trial provided the first head-to-head comparison of endocrine therapy plus palbociclib

vs. chemotherapy in premenopausal MBC patients.[60] This study randomized 189 premenopausal women to receive either OFS plus exemestane plus palbociclib or capecitabine, and demonstrated a significantly increased progression-free survival (PFS) in the endocrine therapy-based arm (HR: 0.66, 95%CI: 0.44-0.99).[60]

Following these results, endocrine therapy with an aromatase inhibitor and OFS plus a CDK4/6 inhibitor should be preferred over chemotherapy as the standard upfront treatment in young women with HR+/HER2-negative metastatic disease, including young patients with dnMBC.[11]

New Therapeutic Options in Young Women With dnMBC: Germline BRCA-Mutant Breast Cancer

The prevalence of germline *BRCA1/2* mutations is estimated to be about 5%-10% among unselected breast cancer population; however, such prevalence is reported to increase up to 18% in breast cancer patients aged ≤40 years.[11,41,42] Compared with sporadic tumors, *BRCA*-mutant breast cancers have an impaired homologous recombination DNA repair mechanism, implying higher genomic instability and consequent higher sensitivity to DNA-damaging agents.[43,61,62]

In the last 3 years, several therapeutic options have been implemented to exploit defects in the DNA repair pathways in order to achieve synthetic lethality in *BRCA*-mutant breast cancer cells.

The TNT trial proved the clinical utility of platinum agents in triple negative *BRCA*-mutant metastatic tumors. This trial randomized metastatic TNBC patients, regardless of *BRCA1/2* mutational status, to receive 6 cycles of either carboplatin or docetaxel.[43] A comparable efficacy, with better toxicity profile for carboplatin over docetaxel in the *BRCA*-mutant cohort was observed,[43] making it a suitable alternative chemotherapeutic option.

The pivotal randomized phase III trials OlimpiAD and EMBRACA demonstrated the efficacy of the PARP inhibitors olaparib and talazoparib, respectively, in *BRCA*-mutant HER2-negative MBC.[61-64] Both trials compared the PARP inhibitor to a non-DNA-damaging chemotherapy of physician's choice (namely eribulin, capecitabine, vinorelbine and gemcitabine). In both RCT, the PARP inhibitor showed to significantly improve PFS (the primary endpoint), with no significant improvements in OS.[61-64]

The BROCADE-3 trial addressed the efficacy of PARP inhibition with veliparib in combination with carboplatin and paclitaxel in the first-line to third-line treatment of germline *BRCA*-mutant HER2-negative MBC.[65] This trial demonstrated a significant improvement in PFS with the addition of a PARP inhibitor to a highly active chemotherapy backbone.[65]

Notably, a phase II trial recently showed promising activity of PARP inhibition in MBC patients with either somatic mutations in *BRCA1/2* genes or germline pathogenic variants in homologous recombination genes other than *BRCA1/2* (Ie. *PALB2*), significantly expanding the population of patients who could potentially benefit from genetic testing in the metastatic setting.[66]

Taken together, these data demonstrate the clinical utility of genetic testing to inform treatment choices in young patients with HER2-negative metastatic breast cancer, and underline the importance of offering genetic counselling as soon as the diagnosis of metastatic disease is ruled out. This approach might be particularly challenging in young patients with dnMBC, for whom genetic counselling comes right after the diagnosis of an incurable disease. Future studies will have to elucidate the optimal therapeutic sequence in this patient population, expecially in those patients with *BRCA*-mutant TNBC, for whom chemoimmunotherapy, carboplatin and PARP-inhibitors represent all valuable first-line therapeutic options.[67,68]

Loco-Regional Treatment of the Primary Tumor

The optimal loco-regional treatment of the primary tumor represents another challenge in the management of patients with dnMBC.[69]

Results from restospective studies and randomized clinical trials addressing this topic have been contradictory.[70-73] A large meta-analysis of retrospective evidences showed a significant positive association between longer survival and surgical resection of primary tumor.[74] However, the interpretation of these results is limited by the presence of multiple selection biases.[70–73]

Most randomized trials have shown no significant clinical benefit of loco-regional treatment of the primary tumor in dnMBC,[75-78] with a potential detrimental effect on survival in aggressive breast cancer subtypes.[75-78] One large randomized trial (n = 274) showed a significant improvement of about 9 months in median OS favoring the loco-regional treatment.[77] An unplanned subgroups analysis showed that the patients with the greatest benefit from surgery were those younger (<55 years), with bone-only metastasis and favorable tumor biology (HR+/HER2-negative). However, treatment arms were imbalanced with respect to breast cancer subtypes, and the greater proportion of TNBC patients in the no-surgery arm represents a potential confounding factor. The E2108 trial represents the most recent and largest trial investigating the efficacy of loco-regional treatment in dnMBC. This trial enrolled 390 women with dnMBC, of whom those who had no disease progression after 4-8 months of systemic therapy were randomly assigned to either systemic therapy alone or to local treatment. The trial failed to demonstrate a significant difference in OS.[75] Patients with TNBC appeared to have worse OS with local treatment, although this difference was not significant, probably due to the small number of patients. Importantly, loco regional recurrence/progression was significantly lower in the loco regional treatment arm (3-year rate 10.2% vs. 25.6%). However, this did not translate in a significant improvement in health-related quality of life (QoL).

On the basis of these current evidence, surgery of the primary tumor cannot currently be considered a standard therapeutic approach in patients with dnMBC. Nevertheless, the availability of new effective systemic treatments for distant disease control, such as CDK4/6 inhibitors, warrants further evaluation on the role of primary surgery in a contemporary population of dnMBC patients.

In light of the clinical benefit observed in some trials in young dnMBC patients with more indolent breast cancer subtypes, this strategy could now be considered in selected cases after a careful discussion within a multidisciplinary team, and taking into account that young dnMBC patients have been underrepresented in these trials.[10]

Quality of Life in Young Women Living With Metastatic Breast Cancer

In women with MBC, improved QoL has shown a positive association with longer survival.[79] For this reason, maintaining health related quality of life (HRQoL) has become paramount in this setting, especially in those patients who could attain long-term disease control with current treatments, including young dnMBC.

Nevertheless, living with metastatic cancer is still associated with multiple challenges that negatively impact on the QoL, especially in long survivors.[80,81] The process of adaptation to a cancer diagnosis is even more burdensome for young patients with dnMBC. In this population, cancer-related and treatment-related side effects elicit alterations of self-perception and of social, emotional and sexual functioning that lead to a higher deterioration of HRQoL.[82-84] Another factor that can impact on the HRQoL of young dMBC patients is the hampering of long-term life projects based on reproduction.[85-87] Finally, the psychological burden of metastatic cancer is also directly related to the uncertainty of the prognosis.[88]

There is a compelling body of evidence on the psychological burden related to breast cancer survivorship, but less has been published on how to mitigate it. A Cochrane review of 10 randomized clinical trials has shown a small but significant impact of psychological intervention on OS, with a limited improvement in some psychological symptoms.[89] Recently, a randomized clinical trial reported that mindfulness and survivorship education are effective in reducing depressive symptoms, fatigue and sleep disturbance in young patients.[90] However, the trial included only women with early breast cancer, further highlighting the need for clinical research specifically aimed at increasing HRQoL in young patients with dnMBC.

HRQoL is also influenced by the occurrence of cancer-related symptoms than can be effectively mitigated by anti-cancer medications. In the MONALEESA-7 trial, ribociclib significantly delayed time to deterioration (TTD) of HRQoL measured via patient-reported outcomes.[91] Furthermore, patients treated with ribociclib experienced longer TTD for subdomain of the questionnaires that are especially distressing for young women such as pain, fatigue and physical, emotional and social functioning. In the YoungPEARL trial, both endocrine therapy and chemotherapy maintained HRQoL, defined by QLQ-C30 score, and no differences in TTD for global HRQoL was observed.[92] Chemotherapy maintained global QoL over time but at the cost of typical adverse events that significantly impact on physical functioning, while endocrine therapy was associated with a trend for increased insomnia, suggesting that even with endocrine treatment adverse events are not infrequent and should be carefully managed.

The disruption of long-term life projects based on reproduction represents another challenging issue which inevitably affects the QoL of young patients with dnMBC. In young women with dnMBC, concerns regarding fertility preservation and family planning should be promptly addressed,[10,11] as inadequate counselling on this topic has been associated with higher rate of depression.[93] However, oncofertility counselling can be troublesome in this setting. Although new effective treatments can allow long-term survivals in these patients, dnMBC remains an incurable disease whose prognosis is uncertain and requires continuous treatment. For this reason, oncofertility counselling must also include careful and appropriate information on disease prognosis, life expectancy and potential consequences of pregnancy, including the prolonged interruption of ongoing effective treatments.[10,94]

Summarizing, young women affected by dnMBC present with an increased risk of QoL deterioration related to psychological burden, cancer-related symptoms and significant alteration in social and role functioning. For women with early breast cancer, multiple interventions, both pharmacological and non-pharmacological, have been studied to reduce the psychological and physical effects of cancer treatments.[95] Even though some of these strategies have been evaluated in young women with *de novo* metastatic disease, there is a paucity of data that warrants further research on this topic.

Conclusions

The diagnosis of dnMBC arising at young age represents a challenging situation for both patients and clinicians. While it is true that young women with dnMBC usually have better treatment responses and prognosis, an evidence-driven management is crucial to maximize the chances of attaining both long-term survival and acceptable QoL. Despite no specific recommendations are currently available, recent studies have added important evidence for the optimal management of young patients with dnMBC, especially with regard to HR+ disease, genetic testing and loco-regional treatment of the primary tumor.

Further dedicated studies or pre-planned subgroup analyses from clinical trials are needed to improve cancer care in this patient population.

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