Review Article

Management of *BRCA* mutation carriers

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Abstract: Pathogenic mutations in two autosomal dominant genes, *BRCA1* and *BRCA2*, with high penetrance are supposed to be the cause for an approximated 5–7% risk of all breast cancer (BC) and ovarian cancer (OC). Compared to sporadic BC, *BRCA* mutated (*BRCA*mut) BC differs for lifetime risk of onset and sensitivity to systemic therapies. A hereditary BC syndrome should be taken into account when there are numerous relatives with BC early-onset (typically before menopause). Moreover, *BRCA*mut carriers showed a lifetime possibility of manifesting OC. When a BC diagnosis is made in young patients or in suspicious personal relatives' anamnesis, be aware of being carriers of a *BRCA* mutation may influence the decision making-process about surgical procedure and prevention strategies. In this review, we examined surgical treatment choice for *BRCA*mut BC, risk of ipsilateral breast recurrence (IBR) and contralateral breast cancer (CBC). We examined the role of breast-conserving therapy (BCT), risk-reducing mastectomy (RRM) and preventive risk-reducing salpingo-oophorectomy (RRSO) with a special consideration about advantage in terms of mortality reduction for both conservative and prophylactic measures. We also reviewed the sensitivity of mutated BC to platinum-based antineoplastic drugs and poly (ADP-ribose) polymerase inhibitors (PARPi) by emphasizing the results of clinical trials recently published.

Keywords: Breast cancer (BC); *BRCA* mutation; risk-reducing surgery; poly (ADP-ribose) polymerase inhibitors (PARPi); platinum compounds

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Introduction

An inherited pathogenic mutation in *BRCA* genes causes an enhanced lifetime possibility of manifesting breast cancer (BC) and ovarian cancer (OC). Operative prophylactic strategies have been performed making genetic counselling an indispensable part of the management of these patients. Approximately 5% of all BC and 15–20% of hereditary BC depends on *BRCA1* or *BRCA2* gene mutations. According to current evidence, 55–65% of *BRCA1*mut and 45% of *BRCA2*mut carriers will manifest BC by 70 years. Nowadays, *BRCA*mut BC could receive new therapeutic approaches. We review the current effective risk-reducing therapy and we show the future research prospects.

BC and mutation: surgery

Risk-reducing mastectomy (RRM)

Bilateral RRM seems to decrease the estimated lifetime risk of developing BC by more than 90% among *BRCA* mutation patients (1-10).

Domchek *et al.* (1) found that RRM decreased the lifetime possibility of manifesting BC in *BRCA*mut. After 3 years of follow-up period (FUP), no women treated with RRM manifested a BC, compared to 7% of patients without RRM who experienced a BC. Furthermore, risk-reducing salpingo-oophorectomy (RRSO) decreases the possibility of BC in both *BRCA1* (HR =0.63; 95% CI: 0.41–0.96) and *BRCA2* (HR =0.36; 95% CI: 0.16–0.82) mutation carriers with no personal history of BC. A risk reduction effect in BC among *BRCA1* patients with RRSO before 50 years (HR =0.51; 95% CI: 0.32–0.82) has been noticed, but no advantages were observed in those with RRSO after 50 years (HR =1.36; 95% CI: 0.26–7.05) (1).

Rebbeck *et al.* (2) found that bilateral prophylactic mastectomy (BPM) decreased the risk of BC in patients without prior RRSO by 90% (HR =0.09; 95% CI: 0.02–0.38); only 2 patients out of 105, with prior RRM, experienced a BC (mean FUP of 5.3 years). In women with concurrent or prior RRSO, the BC risk-reduction was more considerable (HR =0.05; 95% CI: 0.01–0.22).

Hartmann *et al.* (3), in a retrospective cohort study, found that bilateral RRM decreased the incidence and mortality of BC in both the moderate- and high-risk groups by 90%. These advantages must be evaluated carefully; current studies have advised that much of the gain of bilateral salpingo-oophorectomy (BSO) on BC risk might be derived to selection bias rather than a true gain (11).

Mortality benefit

Two recent studies (mean FUP of 13.3 and 8.5 years, respectively) evaluated the impact of bilateral RRM in *BRCA* carriers on mortality (6,7). Ingham *et al.* found that BPM wasn't significantly linked with reduced death for all causes (HR =0.226; 95% CI, 0.05–1.016). Heemskerk-Gerritsen *et al.* found that BC specific mortality was also not significantly decreased (HR =0.29; 95% CI: 0.03–2.61). The BC reduction-risk with bilateral RRM, nevertheless, has not brought benefits in terms of survival, since longer follow-up are needed.

In a decision analysis, Schrag *et al.* (12) correlated RRM and RRSO with no risk-reducing strategies among *BRCA* mutation carriers. They created hypothetical cohorts of patients using early estimates of the cumulative risk of BC among *BRCA*mut to calculate the effect of prophylactic strategies on survival. The authors calculated this risk by a Markov model. This study found a considerable gain in life expectancy with RRM than RRSO. Anyway a gain in life expectancy of 4 years does not mean that every patient will earn 4 years of life.

Contralateral prophylactic mastectomy (CPM)

BRCA carriers have an enhanced rate of contralateral breast cancer (CBC). In a meta-analysis of 11 studies (7 cohort and 4 case-control studies), including 807 carriers and 3,163 non-carriers, Valachis *et al.* (13) asserted that the rate of CBC for *BRCA* carriers was 23.7% (95% CI: 17.6–30.5%) while for non-carriers was 6.8% (95% CI: 4.2–10%). *BRCA* carriers had an enhanced rate of CBC compared with controls [response rate (RR) =3.56; 95% CI: 2.50–5.08; P<0.001]. *BRCA1*mut carriers presented an enhanced probability of manifesting CBC compared to *BRCA2*mut (21.1% for *BRCA1*mut *vs.* 15.1% for controls). In this meta-analysis only RRSO (RR =0.52; 95 % CI: 0.37–0.74) and age >50 years old seem to reduce, statistically, the risk for CBC. Moreover, a recent study (14) asserts that women with a BC diagnosis before 41 years showed a 10-year possibility of manifesting a CBC of 23.9%, while those with a diagnosis between 41 and 49 years had a risk of 12.6%.

Mortality benefit

There are limited data about the efficacy of CPM to improve survival in *BRCA1/2* carriers. Two studies (15,16) (mean FUP of 4.3 and 3.4 years, respectively) reported data on breast cancer specific survival (BCSS) in *BRCA* carriers after RRM *vs.* therapeutic mastectomy while only one (16) on overall survival (OS). There was no disparity in BCSS between *BRCA* carriers who underwent CPM and those who didn't (HR =0.78; 95% CI: 0.44–1.39; P=0.40). A single study (16) showed a 94% OS for RRM group *vs.* 77% for controls (P=0.03). Anyway, if adjusted for other factor as RRSO, carriers in the first group didn't reach an enhancement in terms of survival than those in the second group (P=0.14).

Metcalfe *et al.* (17) in a recent retrospective analysis conclude that *BRCA* mutated (*BRCA*mut) women treated for early stage BC who underwent bilateral mastectomy presented an enhanced risk for death for BC compared to women who underwent unilateral mastectomy. At 20 years the survival rate for patients with contralateral mastectomy was 88% *vs.* 66% for those who didn't. After controlling for age at diagnosis and therapy, contralateral mastectomy showed a decreased risk of death for BC by 48% (HR =0.52; 95% CI: 0.29–0.93; P=0.03).

Breast-conserving therapy (BCT) in BRCAmut

Breast conserving surgery (BCS) followed by radiotherapy (RT) is currently considered the gold standard approach in early-stage sporadic BC (18,19). There is a paucity data about the use of a conservative strategy in *BRCA* carriers.

Ipsilateral breast recurrence (IBR), CBC and survival after BCT in BRCAmut

The rate of ipsilateral recurrence following BCT is higher in *BRCA* mutation patients. IBR is also higher in *BRCA*mut treated with BCT than those treated with mastectomy (*Table 1*).

In 2002, Haffty *et al.* (20) reported high rates of IBR and CBC following BCT in *BRCA*mut. From 1975 to 1998, they studied 290 women (105 with sporadic BC and 22 with genetic predisposition) with BC before 42 years treated with BCT. After 12 years of FUP, *BRCA* carriers showed an increased rate of IBR (identified as second BC in mostly cases) (49% *vs.* 21%, P=0.007) and CBC (42% *vs.* 9%, P=0.001) than controls. However, there are bias in this study: none of the three women of genetic group with positive oestrogen receptor (ER)/progesterone receptor (PR) status were treated with adjuvant hormonal therapy; dead patients were excluded from this database; 19 patients (14.9%) had no axillary surgery despite only 10 cases (5.8%) are tumour *in situ*; surgical margins status were unknown in 50% of *BRCA* mutation carriers. No data on BCSS and OS were reported.

In 2007, Brekelmans *et al.* (15), between 1980 and 2004, studied 103 *BRCA2*, 223 *BRCA1* and 311 non-*BRCA* BC women. The IBR rate was the same between carriers and non-carriers following BCT (16% and 17% for *BRCA1* and *BRCA2*, respectively; 15% and 21% for non-*BRCA* hereditary BC and sporadic BC patients, respectively). The 10-year actuarial risk to develop a CBC was higher in *BRCA*mut (25% for *BRCA1*mut and 20% for *BRCA2*mut) compared with non-*BRCA*mut hereditary BC and sporadic BC patients (6% and 5%, respectively; P≤0.001 compared with *BRCA2* associated cancers). OS and BCSS were the same between groups. On multivariate analysis, the administration of adjuvant chemotherapy and RRSO, but not CPM (or bilateral mastectomy), were the only prognostic factors for BCSS in BC *BRCA*-related.

In 2009, Garcia-Etienne *et al.* (21), between 1994 and 2007, studied 54 *BRCA* carriers with BC and 162 sporadic BC who underwent BCT (4 years of follow-up). After 10 years IBR and CBC rates were 27% and 25% for carriers, 4% and 1% for sporadic cancer (P=0.03), respectively. We need to consider that 8 of 11 (73%) women with IBR (n=6) or CBC (n=5) performed genetic test after breast recurrence.

In 2010, Pierce *et al.* (22), studied 655 *BRCA* carriers with BC who underwent breast conservative surgery plus RT (n=302) or mastectomy (n=353). Estimated IBR rates were greater at all-time points in patients who underwent breast conservative therapy than those who underwent mastectomy: 4.1% *vs.* 1.4% at 5 years, 10.5% *vs.* 3.5% at 10 years and 23.5% *vs.* 5.5% at 15 years. Hormonal therapy seems to reduce the rate of IBR principally in *BRCA2* carriers (*BRCA*: P=0.08; *BRCA1*: P=0.13). CBC rates was similar in patients treated with or without adjuvant RT (P=0.44), supposing that RT has no influence on CBC. The 10 and 15 years risk of BCSS after BCT was 93.6% and 91.7%, while after mastectomy was 93.5% and 92.8%, respectively (P=0.85). The 10 and 15 years risk of OS after BCT was 92.1% and 87.3%, while after mastectomy was 91.8% and 89.8%, respectively (P=0.73). The evidence of an infiltrating lobular cancer (HR =4.3; P=0.01) and the growth of a CBC (HR =2.5; P=0.02) were linked to breast cancer-specific mortality (BCSM). About OS the growth of OC was related to enhanced rates of death (HR =5.0; P=0.0001).

In 2011, Metcalfe *et al.* (30), between 1975 and 2008, studied 396 *BRCA*mut BC treated with BCT. The 5- and 10-year risk of IBR was 5.8% (95% CI: 3.2–8.4%) and 12.9% (95% CI: 8.7–17.1%). Three factors reduced the rate of IBR: adjuvant chemotherapy (70.2%, RR =0.45; 95% CI: 0.24–0.84; P=0.01), RT (87.4%, RR =0.28; 95% CI: 0.12–0.63; P=0.002), salpingo-oophorectomy (33.3%, RR =0.33; 95% CI: 0.13–0.81; P=0.02).

In 2011, Metcalfe *et al.* (29), between 1975 and 2008, studied the CBC risk in 810 *BRCA*mut BC who underwent BCT or mastectomy. In total, after a median FUP of 11.1 years, 149 (18.4%) manifested a CBC, with a median FUP of 5.7 years (range, 0.2–15 years) between first BC and CBC. The 5-, 10- and 15-year risk of CBC was 13.1% (95% CI: 10.3–15.9%), 22.0% (95% CI: 19.2–26.8%), and 33.8% (95% CI: 28.6–39.0%), respectively. The annual risk was 2.1%. Carriers with BC diagnosed at age 50 years or older manifested a decreased possibility to develop a CBC than those diagnosed at age 40 years or younger (RR =0.47; 95% CI: 0.47–0.82; P=0.008). Women who underwent salpingo-oophorectomy had a decreased risk of CBC, than those with intact ovaries (RR =0.48; 95% CI: 0.27–0.82; P=0.002). This

Table 1 Selected studies with ipsilateral breast recurrence, contralateral breast cancer, breast cancer specific survival and overall survival in BRCA-mutation carriers and breast cancer treated with breast-conserving therapy or mastectomy

Study (year)	Study design	Groups	n	Surgery type	Median follow-up (years)	IBR		CBC		BCSS (%)	OS (%)
						%	P value	%	P value		
Haffty *et al.* (20)	RC	*BRCA1/2*	22	BCT	14–12.8	49	0.007	42	0.001	NR	NR
		Non-*BRCA*	105			21	–	9			
Brekelmans *et al.* (15)	RCC	*BRCA1*	223	BCT or Mast	4.3–5.1	16	NS	25	NS	62	50
		BRCA2	103			17		20		68	61
		Non-*BRCA*	311			15		6	0.001	70	66
		Sporadic	759			21		5	<0.001	59	55
Garcia-Etienne *et al.* (21)	RCC	*BRCA1/2*	54	BCT	4	27	0.03	25	0.03	NR	NR
		Non-*BRCA*	162			4	–	1	–		
Pierce *et al.* (22)	RCC	*BRCA1/2*: BCT *vs.* Mast	302	BCT	8.2	10.5	0.0001	23 (after 8 years)	NA	93.6	92.1
			353	Mast		3.5	–			93.5	91.8
			302	BCT	8.9	23.5	0.0001			91.7	87.3
			353	Mast		12.9	–			92.8	89.8
Chappuis *et al.* (23)	RC	*BRCA1/2*	32	BCT or Mast	6.4	6.2	NR	9.4	NR	NR	NR
		Non-*BRCA*	170			6.5		1.2			
El-Tamer *et al.* (24)	RC	*BRCA1/2*	21	BCT	4.2	19.0	0.05	23.33–19.5	0.05	NR	79.4-94.7
			30	Mast		3.3	NS				
		Non-*BRCA*	220	BCT		5.91	0.05	12.39			77.1
			216	Mast		3.7	NS				
Eccles *et al.* (25)	RC	*BRCA1/2*	72	BCT	6.1–8.7	22.2	NS	35.9	<0.001	NR	Similar
			70	Mast		14.3					
		Non-*BRCA*	83	BCT		24.1		16			
			79	Mast		16.5					
Kirowa *et al.* (26)	RCC	*BRCA1/2*	27	BCT	13.4	48.1	NS	40.7	<0.0001	NR	Similar
		Non-*BRCA*	261			25.3		11.1			
Robson *et al.* (27)	RC	*BRCA1/2*	56	BCT	9.7	12.5	NS	26.8	<0.0001	67.8	NR
		Non-*BRCA*	439			7.9		7.9		86.1	
Robson *et al.* (28)	RC	*BRCA1/2*	87	BCT	1-18	13.6	0.04	37.6	<0.0001	96.9	95.6
Metcalfe *et al.* (29)	RC	*BRCA1/2*	810	BCT or Mast	11.5	NR	NA	22	NA	NA	78.8
Metcalfe *et al.* (30)	RC	*BRCA1/2*	396	BCT	10.5	12.9	NA	NR	NA	NA	81.1

RC, retrospective cohort; RCC, retrospective case-control; IBR, ipsilateral breast recurrence; CBC, contralateral breast cancer; BCSS, breast cancer specific survival; OS, overall survival; BCT, breast-conserving therapy; Mast, mastectomy; NA, not applicable; NR, not recorded; NS, not significant.

reduction was significant in those diagnosed at 50 years or younger (RR =0.39; 95% CI: 0.23–0.67; P=0.0006).

Valachis *et al.* (13) identified two protective factors against IBR in *BRCA*mut: the administration of adjuvant chemotherapy (RR =0.51; 95% CI: 0.31–0.84), and RRSO (RR =0.42; 95% CI: 0.22–0.81).

Prophylactic bilateral RRSO

RRSO is recommended for *BRCA*mut by the age of 35 to prevent BC and OC, while no evidence are seen about its influence on survival in patients with BC associated to a *BRCA* mutation (31-33).

Finch *et al.* (34) found that RRSO decreased by 77% the all-cause mortality before the age of 70 in *BRCA* carriers. This reduction was evident in patients with prior BC (HR =0.31; 95% CI: 0.24–0.39) especially in *BRCA1*mut (HR =0.21; 95% CI: 0.12–0.37). Domchek *et al.* (1) documented an OR of 0.35 (95% CI: 0.19–0.67) for salpingo-oophorectomy and BCSM among patients with prior BC.

In another retrospective study of the 676 patients with stage I–II BC, 345 performed salpingo-oophorectomy after BC diagnosis and 331 preserved intact ovaries. The 20-year OS was 77.4%. The adjusted HR for death for BC in patients with RRSO was 0.38 for *BRCA1* carriers (95% CI: 0.19–0.77; P=0.007) and 0.57 for *BRCA2* carriers (95% CI: 0.23–1.43; P=0.23). The HR for BCSM was 0.76 (95% CI: 0.32–1.78; P=0.53) in patients with ER-positive BC and 0.07 (95%CI: 0.01–0.51; P=0.009) in patients with ER-negative BC. We can conclude that salpingo-oophorectomy decreases mortality in patients with *BRCA1*-associated BC. Women with *BRCA1* ER-negative BC should undergo salpingo-oophorectomy after diagnosis (35).

BC and *BRCA* mutation: therapy

BRCA mutated locally advanced breast cancer (LABC) and metastatic breast cancer (MBC): clinical management and new evidence

Patients harbouring *BRCA1* or *BRCA2* (*BRCA1/2*) gene mutations are responsible for approximated 5% of all BC (36) and approximately 15–20% of hereditary BCs (37). According to recent assessments, 55–65% of *BRCA1* carriers and around 45% *BRCA2* carriers will develop BC by the age of 70 years (38). Actually, there are no definitive guidelines on the optimal chemotherapy for these patients, but there is increasing evidence of enhanced sensitivity to specific drugs in this patient population.

*BRCA*mut could show a pronounced sensitivity to platinum-based antineoplastic drugs probably due to their DNA-damaging mechanism of action. There is a paucity of data about the clinical efficacy of these agents in *BRCA* carriers in the metastatic setting (39), such as in triple negative breast cancer (TNBC) (40). In neoadjuvant setting, series reported a RR increase of 26% in positive family history and 23% in *BRCA*mut patients with platinum-based treatment. In the metastatic setting, prospective studies reported RR in a range from 10% to 40% when cisplatin or carboplatin were included (41,42).

Tamoxifen

In prospective trials, tamoxifen decreased the risk of BC and CBC in patients at high risk (43,44). An analysis of the National Surgical Adjuvant Breast and Bowel Project identified 19 *BRCA1/2* mutations among 288 women with BC (45). Five of 8 *BRCA1* carriers had taken tamoxifen *vs.* 3 of 11 *BRCA2* carriers. Although the sample size was small, this analysis showed a decrease in BC incidence by 62% for *BRCA2* carriers without effective benefit in *BRCA1* carriers.

Narod *et al.*, in a case-control study, analysed the efficacy of treatment with tamoxifen and the possibility of developing a CBC in *BRCA*mut comparing patients with bilateral and unilateral BC (46). Sixty-four *BRCA1* mutation carriers (13%) used tamoxifen *vs.* 39 *BRCA2* mutation carriers (33%). This difference was expected because *BRCA1*-associated BCs are typically ER-negative and *BRCA2*-associated BCs are commonly ER-positive. Tamoxifen seems to be protective against CBC, with OR of 0.38 in *BRCA1*mut and 0.63 for *BRCA2*mut. The combined risk reduction for *BRCA* mutation carriers was 50%. This study also revealed a decrease in CBC in women who underwent RRSO (OR of 0.42), similar to the risk-reduction with tamoxifen.

LABC

A German group presented data from GeparSixto related to *BRCA* mutation and family history of BC or OC. Mutation in *BRCA1/2* genes was evaluated in 94% of patients with TNBC from 315. An increase of 26.7% in polymerase chain reaction (pCR) was observed with addition of carboplatin in patients with a positive relatives' anamnesis for BC or OC despite absence of *BRCA* mutation (pCR: 49%). In patients' *gBRCA1/2* mut, the increase in pCR rate was 23.2% (pCR:

55%). Therefore, mutations in *BRCA1/2* and family history for BC or OC are strong predictors for improvement in pCR rates after carboplatin in TNBC (47).

An adaptive study published in 2016 from Rugo *et al.* (I-Spy2), matched experimental regimen with veliparib in addition to carboplatin with responding cancer subtype (*gBRCA*mut). This study revealed that the addiction of veliparib and carboplatin to usual chemotherapy produced higher rates of PCR compared to usual chemotherapy regimens (pCR: 51% *vs.* 26%) (48).

Studies are ongoing with talazoparib (NCT02282345), olaparib (PARTNER NCT03150576) and veliparib (NCT01818063).

MBC

In a phase III randomized control trial (RCT) who compared carboplatin and docetaxel in *BRCA*mut metastatic or recurrent LABC, overall RR was 68% in those treated with carboplatin *vs.* 33.3% in those with docetaxel with a progression free survival (PFS) of 6.8 *vs.* 3.1 months, respectively (49).

The TBCRC009 study evaluated the efficacy of cisplatin 75 mg/mq d1q21 or carboplatin (AUC 5) d1q21, according to clinical choice in pre-treated MBC. RR was 25.6% (95% CI: 16.8–36%) and was higher with cisplatin (32.6%) compared with carboplatin (18.7%). RR was 54.5% *BRCA1/2* carriers (n=11) (50).

Keeping in mind current evidence, most of the ABC2 panel promoted the inclusion of platinum-containing regimens in the treatment of *BRCA* carriers pre-treated with anthracyclines and taxanes and proved to be endocrine-resistant (51).

A promising area of clinical research is the investigation of poly (ADP-ribose) polymerase inhibitors (PARPi) in treating *BRCA* MBC

Olaparib

In a phase II RCT, 54 recurrent *BRCA*mut LABC, received olaparib administered orally. In 27 women, who got the maximum tolerated dose of 400 mg twice daily, the overall response rate (ORR) was 41% (52). A following multicenter phase II RCT studied the efficacy of olaparib in 298 heavily pre-treated *BRCA1/2* mutated with recurrent solid cancers. The ORR was 12.9% (8 of 62 BC patients), and disease stabilization for at least 8 weeks was showed in 47% of them. The ORR was better for women with no previous exposition to platinum-based antineoplastic drugs (20% *vs.* 9.5%) (53). Gelmon *et al.* (54), in a study with olaparib monotherapy, hypothesized that heavy pre-treatment could decrease the response to olaparib in TNBC associated to *BRCA*mut. Recently, in American Society of Clinical Oncology (ASCO) meeting 2017, Robson *et al.* presented OlympiAD trial compared olaparib as a single agent *vs.* chemotherapeutic agents of physician's choice in late-line MBC. The results showed a clinical and statistical benefit in delaying PFS with olaparib. Three hundred and two patients were randomized of whom 205 received olaparib and 91 received TPC (6 TPC patients were not treated). PFS was significantly longer in those who received olaparib *vs.* TPC (HR =0.58; 95% CI: 0.43–0.80; P=0.0009; 7.0 *vs.* 4.2 months, respectively). Objective response rate was 59.9% and 28.8% in olaparib and TPC arms, respectively (55).

Veliparib

In a phase II RCT presented at the ASCO Annual Meeting 2014, 44 *BRCA*mut MBC received oral veliparib at 400 mg twice daily. When a progression was noticed, it was switched to oral veliparib (150 mg orally twice daily) plus carboplatin. Forty-one women (out of 44) were treated. The partial response rate (PR) was 17% (2 out of 12) in *BRCA1*mut and 23% (3 out of 13) in *BRCA2*mut evaluated at least 4 cycles of follow-up (56).

Niraparib

Studies with niraparib are outstanding. BRAVO is a phase III multicenter RCT that enrols *gBRCA*mut women with HER2 negative BC who received niraparib *vs.* physician's choice (capecitabine, eribulin, gemcitabine, or vinorelbine), excluding women with progressive disease during previous platinum-based therapy (57).

Talazoparib

The ABRAZO phase II trial evaluates the efficacy of talazoparib in *BRCA*mut LABC or MBC women. Patients were randomized in two cohorts: women with MBC responsive to PARPi or women with MBC treated with non-platinum cytotoxic regimens (58). The EMBRACA phase III trial comparing talazoparib 1 mg daily in 21-day cycles *vs.* physician's choice (eribulin or capecitabine or gemcitabine or vinorelbine) (59).

*New chemotherapeutics and activity in BRCA*mut *BC*

About other drugs, new evidence is due to the efficacy of trabectedin and lurbinectedin. In heavily pre-treated MBC patients with *gBRCA* mutations, trabectedin showed a PR of 17% (6 out of 35) and a mean PFS of 3.9 months (60). In the same way, a phase II RCT showed a PR of 14% and mean PFS of 3.3 months (61).

The ORR in 17 *BRCA*mut MBC women treated with lurbinectedin was 41% with a mean response period of 5 months, compared with 9% and 3.3 months of an unselected cohort. An exploratory analysis of 17 women showed a high ORR in *BRCA*mut with no prior exposition to platinum based antineoplastic drugs (64%) (62). At the European Society of Medical Oncology (ESMO) 2016, Balmana *et al.* presented a phase II RCT in which 54 *BRCA*mut MBC received lurbinectedin 7 mg, decreased to 3.5 mg/m^2 intravenous (IV) after 3 weeks. The ORR was 39% and 44% in 7 and 3.5 mg/m^2 dosage group, respectively. More than half were pre-treated with platinum therapy. There was a higher ORR (61% *vs.* 26%), PFS (5.9 *vs.* 2.1 months) and OS (31.8 *vs.* 11.8 months) in *BRCA2*mut compared to *BRCA1*mut. A growing number of studies valuating this drug in women pre-treated with PARPi are underway (63).

Discussion

There are several issues to keep in mind about the management of *BRCA* carriers. When a *BRCA* carrier is identified, the type of BCS must be carefully considered and discussed. Recent, large, multicenter studies have confirmed that BCT is linked with a higher rate of IBR, but no survival advantage has been demonstrated following more radical surgery. Risk-reducing strategies of IBR in carriers who underwent BCT include the administration of adjuvant chemotherapy, RRSO and RT. We can state that the different location, the different histology and the higher FUP period between first cancer and recurrence, compared to sporadic BC, is suggestive for newly diagnosed BC rather than real IBR. The rate of CBC is higher in *BRCA* mutation carriers, and this is the rationale for performing CPM. RRSO can also decrease the rate of CBC in BC associated to *BRCA* mutation. There isn't robust evidence to suggest that the prognosis of these patients with BC is worse than patients with sporadic BC. In addition, BRCA mutation carriers treated with BCT do not have worse overall survival. The prognosis, in fact, is driven by the biological characteristics of the tumour rather than by local treatment. Clinical guidelines about the surgical management of unilateral breast cancer for *BRCA*mut patients are still missing. *BRCA* carriers with BC need to be discussed by a multidisciplinary team keeping in mind that every surgical decision should also take into account the psychological and social impact of every procedure.

Conclusions

Risk-reducing strategies (RRM and/or RRSO) should be proposed to each *BRCA*mut. Data demonstrate similar long-term survival between women with early BC who underwent BCT or mastectomy. However, the enhanced risk of IBR and CBC lead many *BRCA* mutation patients to choose mastectomy with a CPM. If a woman refuses surgical risk-reduction strategies, she should be guided to realize adequate screening tests keeping in mind the known limitations. In mutated patients is possible to use platinum salts during treatment: carriers benefit from this therapy choice. Innovative drugs such as PARPi are an interesting innovative strategy for mutated BC and OC patients where chemotherapy is limited.

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