

Update Breast Cancer 2018 (Part 1) – Primary Breast Cancer and Biomarkers

Update Mammakarzinom 2018 (Teil 1) – primäres Mammakarzinom und Biomarker



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ABSTRACT

This summary provides an overview of how new therapies or new aspects of established therapies relate to the latest findings. Neoadjuvant therapy, local therapy, new aspects of systemic therapy, and prognostic and predictive factors are presented. In the neoadjuvant setting, the association between pathological complete response (pCR) and prognosis is still of interest as is the identification of new molecular predictors

for new therapies such as CDK4/6 inhibitors. As regards surgical treatment, the target is still to reduce the aggressiveness of surgery. To achieve this, a better understanding particularly of ductal carcinoma in situ is required. With regard to systemic therapy, more data on the best combinations and therapy sequences for existing therapies is available. Finally, the use of prognostic and predictive factors may help to avoid over-treatment and ensure that patients only receive therapies which have been shown to be effective for their specific condition and have fewer side effects.

ZUSAMMENFASSUNG

In dieser Übersichtsarbeit wird dargestellt, wie neue Therapien oder neue Aspekte etablierter Therapien in Zusammenhang mit neuesten, aktuellen Erkenntnissen stehen. Neoadju-

vanz, Lokalthherapie, neue Aspekte der Systemtherapie und Prognose- sowie Prädiktivfaktoren werden beleuchtet. In der Neoadjuvanz ist nach wie vor der Zusammenhang zwischen pCR und Prognose von Interesse, ebenso wie neue molekulare Prädiktoren für neue Therapien wie CDK4/6-Inhibitoren zu identifizieren. Bei der operativen Behandlung wird weiter nach einer Reduktion der Aggressivität gestrebt. Insbesondere das duktales Carcinoma in situ muss dafür noch besser verstanden werden. Bei den Systemtherapien wächst die Datenlage zum Verständnis der besten Kombinationen und Therapieabläufe für bestehende Therapieverfahren. Letztendlich muss mithilfe von Prognose- und Prädiktivfaktoren vermieden werden, dass Übertherapien stattfinden und nur die Patientin spezifische Therapien erhält, welche bei dieser individuellen Patientin eine nachgewiesene Wirksamkeit mit wenig Nebenwirkungen haben.

Introduction

In recent decades a number of major medical advances have improved the treatment of primary breast cancer [1–3]. Particularly the attempts to create targeted therapies for molecular subgroups appear to be very promising; the goal is to be as effective as possible while keeping side effects to a minimum and only treating patients who will actually benefit from a specific therapy. A few studies carried out in an adjuvant setting and which included tens of thousands of patients were unable to show a prognostic benefit, indicating that there is still a long way to go. A better understanding of prognostic and predictive factors would be useful to plan new intelligent studies.

The basic treatment approaches for primary breast cancer and the prognostic and predictive factors based on recently published studies and on data presented at recent conferences (including the San Antonio Breast Cancer Symposium 2017) are discussed in more detail below.

Neoadjuvant Therapy of Primary Breast Cancer

Neoadjuvant therapy has become the standard therapy to treat early breast cancer in certain patient groups [4], although numerous issues are still being investigated in ongoing studies, including the issue of predictive markers [5,6], the choice of the right chemotherapy, and the integration of biological therapies [2,7]. A recently published meta-analysis which compared patients who received neoadjuvant therapy with patients who received adjuvant therapy was able to show that overall survival did not differ between groups and that neoadjuvant therapy offered results equal to those for adjuvant therapy. However patients who underwent neoadjuvant therapy based on historic criteria appear to have a higher risk of local recurrence if they undergo breast-conserving therapy (BCT) [8], although it is not clear whether these findings are transferable to patients treated in accordance with the most recent criteria.

Predictive factors for anti-HER2 therapy in the neoadjuvant setting

In a recent analysis of the NeoALTO trial which reported that the pathological complete response (pCR) rate almost doubled following the addition of lapatinib to trastuzumab, the question of predicting the pCR and event-free survival (EFS) based on CNAs (copy number alterations) was investigated. The results were not surprising as it is the reason why HER2 expression has a higher impact on pCR than its amplification. The higher genomic instability of hormone receptor-positive tumors predicts the higher pCR rate. No specific gene or gene region was identified which would allow EFS to be predicted [9]. New findings on the association between pCR and invasive event-free survival (iDFS) are also available from another study, the CALBG 40601 trial, which looked at a combination of lapatinib and trastuzumab in the neoadjuvant setting. Although the addition of lapatinib only had a marginal impact on pCR, the study found a significant benefit with regard to iDFS. Patients classified as luminal A had the most favorable prognosis. Immune activation as measured by an RNA signature was found to be an independent predictive factor for both pCR and iDFS [10].

Association between pCR and prognosis

An analysis of the I-SPY2 platform trial which investigated the association between pCR and EFS and distant disease-free survival (DDFS) has provided an important data on prediction in the neoadjuvant setting, a topic which has been the subject of ongoing debates since the publication of two landmark articles [11,12]. The analysis showed a significant association between pCR and the survival variables EFS and DDFS, which was present irrespective of the biological subtype or type of therapy. These data once again confirm that the decision by regulatory authorities in both the USA and Europe to take pCR as the endpoint for the expedited approval of new drugs was and is the right one [13]. This was also convincingly confirmed by a recently published analysis from the GeparSepto trial, which showed that the significant pCR benefit resulting from the substitution of weekly paclitaxel by weekly

nab-paclitaxel (which had already been reported in 2016) has now also translated into a significant survival benefit [14].

CDK4/6 inhibitors in the neoadjuvant setting

The neoadjuvant NeoMONARCH trial [15, 16] investigated a chemotherapy-free combination of the CDK4/6 inhibitor abemaciclib and the aromatase inhibitor anastrozole compared to either abemaciclib alone or anastrozole alone. The primary endpoint was a drop in Ki-67 as the parameter for proliferation activity after 14 days of therapy, with values determined by repeat punch biopsy. Both the abemaciclib combined with anastrozole and abemaciclib alone resulted in a stronger drop in Ki-67 compared to anastrozole alone. This was also found to be correlated with clinical response after 16 weeks, indicating that the combination of an aromatase inhibitor and a CDK4/6 inhibitor could be a promising option for neoadjuvant endocrine therapy. The most common side effect of abemaciclib was diarrhea with an incidence of 61.4%, although only 4.9% of cases had grade 3 diarrhea [17].

Loco-regional Therapy of Primary Breast Cancer

More precise assessment of the role of resection margins

In breast-conserving surgery (BCT), complete removal of the tumor is the precondition for a low risk of local recurrence. But the question about the optimal resection margin is controversial and still debated. Both the current S3-guideline and the guideline of the American Society of Oncology (ASCO) consider resection to be sufficient if no tumor tissue is verifiable on the inked edge on the surface of the specimen ("no ink on tumor") [18]. This view is primarily based on a meta-analysis from 2014 which included a total of 33 individual studies [19]. A more recent meta-analysis [20], which included a total of 38 individual studies and data from more than 55 000 patients, confirmed that the rate of local recurrence depends on the resection status (R0, i.e. "no ink on tumor": 3.8% vs. R1: 10.3%). However, compared to the findings of the previous meta-analysis, the rate of local recurrence appears to decrease as the margin increases: while the rate of local recurrence was 7.2% for resection margins of 0–2 mm, the rate of recurrence was only 3.6% for margins of 2–5 mm and 3.2% for margins > 5 mm. Based on the limited validity of retrospective meta-analyses more prospective studies will be needed to answer the question about the optimum resection margin in the context of the respective tumor biology, modern preoperative diagnostic procedures, and adjuvant systemic therapy.

Further decrease in aggressive axillary surgery probable

Since the results of the ASOG Z0011 trial, it is generally accepted that pT1c/pT2/cN0 patients who undergo breast-conserving surgery followed by radiotherapy should not undergo secondary axillary lymph node dissection (ALNE), even if a maximum of two sentinel lymph nodes are affected [21]. The IBCSG 23-01 trial, a prospective randomized study, investigated whether it was feasible to

dispense with subsequent ALNE in patients with micro-metastasis (≥ 2 mm) in one or more sentinel lymph nodes [22]. After a median follow-up of 9.8 years, no difference was found with regard to disease-free or overall survival. The findings of the IBCSG 23-01 trial therefore confirm the results of the Z0011 study and the oncological safety of de-escalating axillary lymph node surgery.

Identification of DCIS patients for anti-hormone therapy

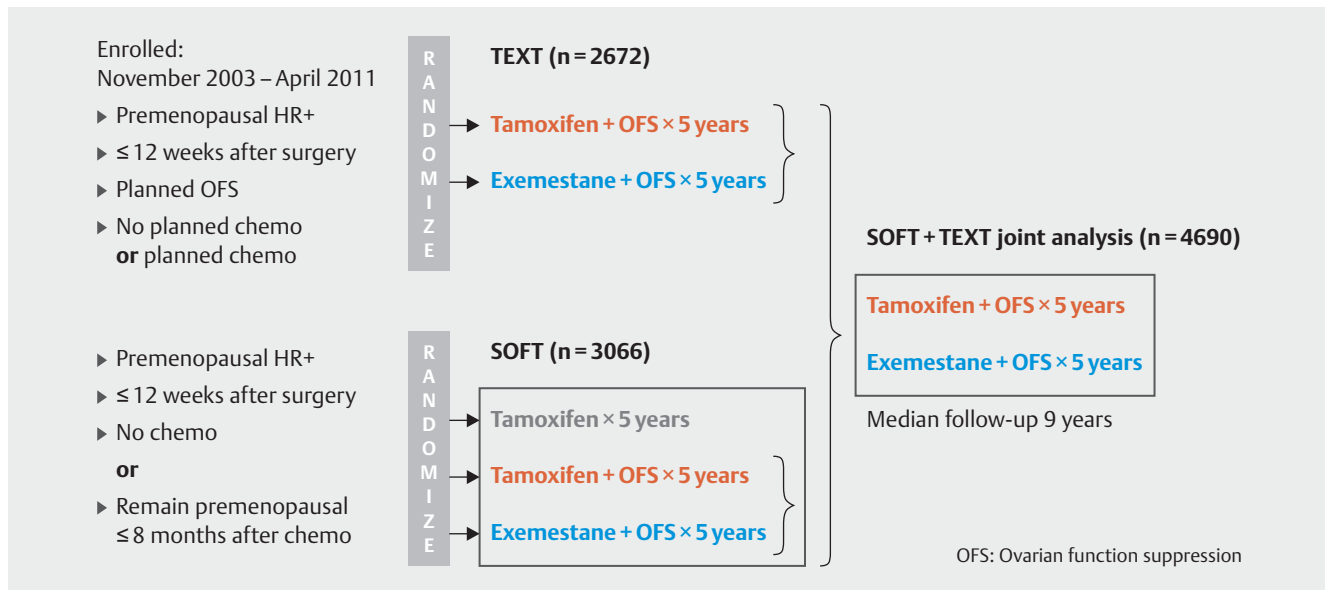
Estrogen is one of the mediators of tumor growth and metastasis. Anti-estrogen therapy, for example with letrozole, is known to stop tumor growth in invasive carcinoma [23]. But such data are not available for patients with ductal carcinoma in situ (DCIS), although the question of whether patients with DCIS should receive anti-hormone therapy and if so, which patients with DCIS should receive it, is currently being discussed. A recent single-arm phase-II trial (CALGB 40903) investigated outcomes after a 6-month therapy with letrozole in a preoperative setting in 55 patients with estrogen receptor-positive ($\geq 1\%$ positive cells in immunohistochemistry) DCIS [24]. The aim of the study was to identify those subgroups who would benefit most from systemic anti-hormone therapy. The selected dependent variable was a lesion with a diameter of between 1 and 7 cm, measurable with MRI. After 3 months of therapy, the average tumor volume as measured with MRI had decreased by 33% (37% volume reduction after 6 months). Moreover, over the course of treatment the expression of estrogen and progesterone receptors and concentrations of the proliferation marker Ki-67 in the tumor were also lower. The study shows that monitoring these biomarkers would offer an ideal basis for identifying patients who would respond to therapy.

New Aspects of Systemic Therapy for Primary Breast Cancer

In addition to developing new therapies and carrying out large therapeutic trials, new aspects of existing therapies are increasingly being investigated as they could help to optimize established therapy regimens, either through introducing prognostic or predictive factors, simplifying therapy regimens, or avoiding side effects.

Changes in Ki-67 concentrations as a predictive marker in anti-hormone therapy

The preliminary findings of the CALGB 40903 DCIS trial were already available for invasive breast cancer [25, 26]. The fact that treatment with aromatase inhibitors reduces Ki-67 levels after 2 weeks in certain patients begs the question whether the reduction measured after two weeks represents a predictive marker for the efficacy of the anti-hormone therapy. This question was investigated in the POETIC trial [27]. The trial randomized 4480 patients. One group received two weeks' treatment with an aromatase inhibitor prior to surgery, the other group did not receive preoperative therapy. Patients in both groups underwent biopsy two weeks before surgery to compare Ki-67 concentrations in the punch biopsy and at surgery. The study confirmed that the aro-



▶ **Fig. 1** Study design of the SOFT and TEXT trials [36].

matase inhibitor down-regulated the expression of Ki-67 [27]. The recurrence rate of patients in whom anti-hormone therapy was unable to down-regulate the expression of Ki-67 was approximately 20%. Given the magnitude of this figure it remains to be seen whether this form of testing is likely to prevail against multi-gene testing.

GnRH confirmed as ovarian protector during chemotherapy

As more and more patients with a good prognosis are identified, interest is increasingly focusing on the side effects of treatment. One of these side effects is the toxicity associated with chemotherapy and its impact on the ovaries of young women who want to have children. One strategy to minimize side effects consists of administering GnRH analogues simultaneously with chemotherapy. This administration is believed to protect the ovaries during chemotherapy. The data of 873 patients from 5 prospective randomized studies were included in a meta-analysis. The meta-analysis showed that the rate of chemotherapy-induced premature ovarian insufficiency was significantly lower in patients who were treated with GnRH analogues compared with women who did not receive GnRH analogues (14.1 vs. 30.9%). The pregnancy rate in the GnRH-treated group was also significantly higher (10.3 vs. 5.5%) [28]. The investigated prognostic parameters showed no differences between the two groups, indicating that oncological safety did not appear to be compromised by the additional administration of GnRH analogues.

In view of these findings, predictors that show which women have a particularly high risk of chemotherapy-induced premature ovarian insufficiency could be useful when deciding whether to administer additional treatment with a GnRH analogue. Potential predictors currently being discussed include anti-Müllerian hormone (AMH) [29] or genetic germline cell variants associated with age at menarche and menopause [30–33].

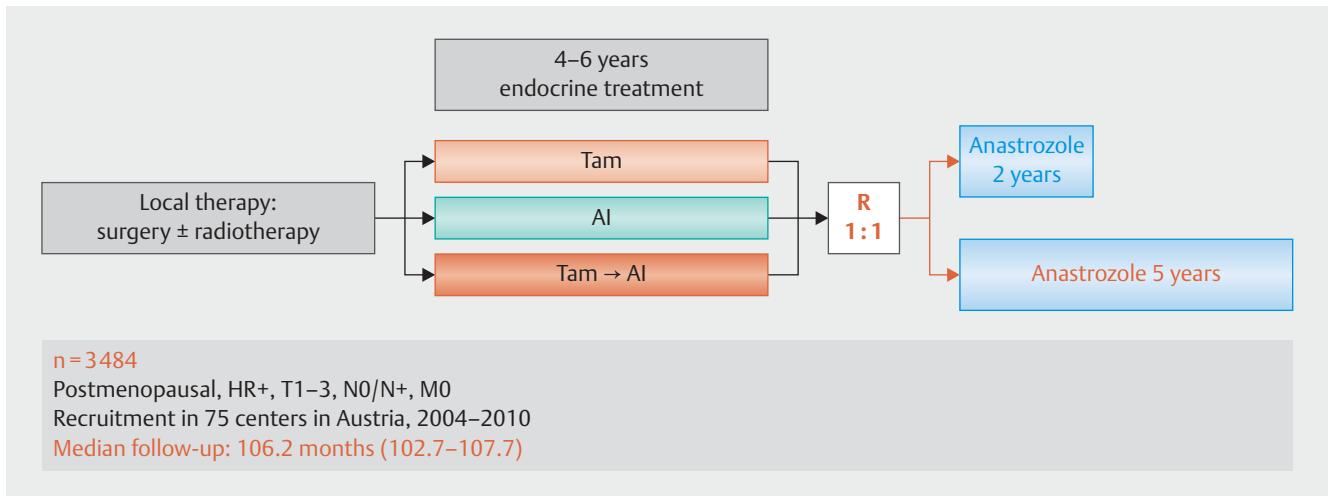
Increasing the dose density in adjuvant chemotherapy reduces the rate of recurrence and mortality

An EBCTCG meta-analysis of 21 000 patients from 16 randomized studies investigated the effect of increasing the dose density in adjuvant chemotherapy [34]. Irrespective of whether the dose density was increased by shortening the intervals between courses or by the simultaneous administration of anthracyclines and taxanes, an increased dose density significantly reduced the rate of recurrence and mortality.

Treatment of Primary Hormone Receptor-positive HER2-negative Breast Cancer

Ovarian suppression and aromatase inhibitors optimal for premenopausal patients?

The optimal anti-endocrine treatment for patients with primary breast cancer is still debated. The question here was whether treatment with an aromatase inhibitor and ovarian function suppression (OFS) is adequate to treat premenopausal, hormone receptor-positive patients or whether they should receive tamoxifen. The first analysis of the SOFT and TEXT trials (▶ **Fig. 1**) showed that breast cancer patients in all subgroups did not benefit from OFS [35]. After a follow-up of 8 years a more recent analysis was published. After the long observation period, a benefit of OFS in terms of recurrence-free survival and overall survival was demonstrated for premenopausal patients compared with patients who did not have OFS. In absolute terms, overall survival improved by 1.9% in the general patient population and by 4.2% in the group of patients who had a high risk of recurrence and received therapy with tamoxifen and OFS [36]. These data could be clinically relevant insofar as OFS could be offered to patients with a high risk of recurrence. In recent years, these patients were in-



► **Fig. 2** Study design of the ABCSG-16 trial [43].

creasingly less likely to undergo OFS because of the inconsistent data and because no improvement in overall survival had been reported. The analysis with the longer follow-up was also able to confirm that treatment with an aromatase inhibitor combined with OFS resulted in a better prognosis than treatment with tamoxifen combined with OFS. The absolute improvement in recurrence-free survival was 4% [36]. Even greater effects were reported for the group of very young women and for the group treated with chemotherapy. However, this still did not translate into a benefit in terms of overall survival. Patients who undergo OFS require careful monitoring with regard to side effects. After one year, 19% of patients who had OFS terminated the treatment compared with 6% of patients who did not undergo OFS [36].

Is extended therapy with an aromatase inhibitor for 2 years after 5 years of anti-hormone therapy sufficient?

When treating postmenopausal patients with primary hormone receptor-positive breast cancer, studies were able to show that treatment with an aromatase inhibitor following 5 years of therapy with tamoxifen led to an improvement in recurrence-free survival [37]. The optimal duration of this so-called extended anti-hormone therapy is still a matter of debate [38], particularly as the published data are inconsistent [38-42]. An Austrian study on this issue was recently published (► **Fig. 2**) [43]. The ABCSG-16 trial randomized 3494 postmenopausal patients with primary hormone receptor-positive breast cancer who had already undergone 5 years' treatment with tamoxifen or a sequence of tamoxifen and an aromatase inhibitor or an up-front aromatase inhibitor either into a therapy arm to receive an aromatase inhibitor for 2 years or a therapy arm to receive an aromatase inhibitor for 5 years. No differences were found between the two groups with regard to recurrence-free survival, overall survival, time to second primary cancer or time to contralateral breast cancer [43]. However, the rate of bone fractures was significantly higher in the group of patients who received an aromatase inhibitor for an additional 5 years (6 vs. 4%) [43]. These data support the suggestion

that 2 years of extended therapy following 5 years of endocrine treatment should be sufficient to have an impact on prognosis. As the data remains inconsistent, a meta-analysis would be useful.

Treatment of Primary HER2-positive Breast Cancer

Duration of trastuzumab therapy – nothing has changed

The treatment of HER2-positive patients with early breast cancer includes the administration of trastuzumab over a total period of 12 months. The HERA trial showed that patients derived no additional benefit from extending the administration of trastuzumab to 24 months [44]. However, the duration of treatment has not been determined empirically. This therefore begged the question whether shorter treatment times might not be just as effective as the standard treatment time. The French PHARE trial carried out a non-inferiority study into the adjuvant administration of trastuzumab for a period of only 6 months compared to the standard therapy of 12 months but failed to show that 6 months' treatment was non-inferior [45]. However there were indications that the benefit of a 12-month treatment was largely limited to those patients who received trastuzumab sequentially with chemotherapy. The explanation for this could be that a synergy effect is created by the parallel administration of trastuzumab and taxanes [46]. The SOLE study [47] therefore set out to investigate whether, after receiving a short trastuzumab therapy of nine weeks in parallel to chemotherapy with docetaxel (3 cycles of 80 or 100 mg/m² every three weeks), it would be possible to then dispense with further trastuzumab therapy. All patients additionally received anthracycline-based therapy with F600/E75/C600 and adjuvant radiotherapy and/or adjuvant endocrine therapy for at least 5 years, depending on the indication. A total of 2176 patients were included in the study. After a mean follow-up of 5 years, the primary endpoint (non-inferiority of 9 weeks treatment with trastuzumab with

regard to disease-free survival) was not achieved (after 5 years, 90.5% of patients who received trastuzumab for 12 months were disease-free compared to only 88.0% of patients who received trastuzumab for 9 weeks; HR: 1.39; 90% CI: 1.12–1.72). Treatment with trastuzumab over a total of 12 months therefore remains the standard approach. Interesting, the subgroup analysis again appeared to show a synergy effect with regard to taxane-based chemotherapy: patients who received docetaxel at a dose of just 80 mg/m² benefited most from the 12 month treatment. Further prospective studies are therefore required to investigate the optimal doses for taxane-based treatment when combined with HER2-targeted therapy.

Biosimilars of trastuzumab – the data is getting stronger

Now that the patent has expired, several biosimilars of trastuzumab are available for HER2-targeted therapies [2]. The molecular structure of these substances is not entirely identical to that of the original active agent. This means that, in contrast to classic generic drugs, more expensive approval procedures are required before these products will be generally available. A biosimilar should not show any significant clinical difference in terms of quality, efficacy and safety compared to the original active ingredient. In a randomized double-blinded study, the biosimilar ABP-980 was compared with the original trastuzumab to treat patients with early, non-metastatic, HER2-positive breast cancer. The study consisted of a neoadjuvant phase (4 cycles combined with paclitaxel) and an adjuvant phase (continuation of the HER2-targeted therapy for up to one year). The data for the neoadjuvant phase were already presented at the 2017 ESMO conference; no differences were found with regard to efficacy (pCR rate) and safety [48]. The safety data for the adjuvant phase was presented at the 2017 San Antonio Breast Cancer Symposium [49]. Once again, no significant differences were found compared to trastuzumab; cardiac toxicity in particular (the incidence of decreased left ventricular ejection fraction was 1–3%) was similar for all therapy arms of the study. It is expected that biosimilars will play an increasingly important role in clinical practice in future. However it is not currently clear which preparations will reach the market, because some pharmaceutical companies are currently involved in patent infringement proceedings against one another [50].

Prognostic and Predictive Factors

Prognostic and predictive factors are necessary to estimate the prognosis of patients and assess the efficacy of the therapy [51, 52]. Several approaches are used in the adjuvant setting to identify patients with an excellent prognosis who do not require chemotherapy. The most advanced approach is to analyze the gene expression of between 10 and 100 genes [53, 54]. But research into using germline and tumor mutations or using the presence of circulating tumor cells or circulating nucleic acids from the tumor as biomarkers is becoming increasingly important [51, 55].

Circulating tumor cells as prognostic markers in long-term follow-up

One prognostic factor that has already been described in the literature is based on the detection of circulating tumor cells (CTCs) in blood prior to adjuvant or neoadjuvant therapy using the CellSearch[®] CTC test [56–58]. Assessing the risk of recurrence several years after primary therapy is clinically relevant as the findings can be used to guide decision-making on whether adjuvant endocrine therapy should continue after more than 5 years have passed. The results of a recently published study are important in this context [59]. The blood of 546 patients from a clinical study into adjuvant chemotherapy (E5103) was examined once for CTCs. The median time between inclusion in the study and blood collection was 5.2 years. At least one CTC was detected in 4.9% of patients. In a multivariate analysis adjusted for clinical risk factors, patients in whom CTCs were detected had an 18.3 times higher risk of recurrence. These results underscore the biological relevance of CTCs even in the non-metastatic setting, although the findings were not compared with results obtained using classic tumor markers. The findings support the results of the SUCCESS A trial [60] which reported that determination of CTCs 2 years after the primary diagnosis offered prognostic information for the course of disease after 2 years.

Germline mutations as prognostic and predictive markers

Increasing attention is also being paid to germline mutations of patients with breast cancer. A prognostic or predictive significance has been established for some genetic variants [61–69]. There is relatively detailed data on the prognostic importance of BRCA1 and BRCA2 mutations for certain groups of patients. The recently published POSH study followed up almost 3000 patients with primary breast cancer who developed breast cancer before the age of 40 years and tested them for BRCA1 and BRCA2 mutations [70]. This study found no difference in survival between groups. These data could have implications for clinical procedures in terms of the surgical treatment of these patients, as the diagnosis would provide enough time to counsel affected women about prophylactic surgery of the contralateral side [71]. A PARP inhibitor has already been approved specifically to treat patients with a BRCA1 or BRCA2 mutation [72]. The PRAEGNANT network in Germany has recently reported on the mutation frequency of BRCA1 and BRCA2 and other panel genes and estimated the relevance of these findings for therapy under “real world” conditions [73]. The germline DNA of 1462 patients with metastatic breast cancer was investigated. A germline mutation in one of the panel genes was identified in 8.4% of cases. The most common mutations were found in genes in the BRCA2, CHEK2, BRCA1, PALB2 and ATM regions. The highest rate of mutations was found in patients with triple-negative and luminal B-like tumors. Patients with mutations had a poorer prognosis compared to the overall patient cohort.

Conclusion

The data presented here offers a good summary of current developments and shows that more and more new therapies are being developed to treat special subgroups and are combined with the use of biomarkers. The second part of this update [74] will provide a summary of recent developments in metastatic breast cancer, supportive therapy, quality of life and prevention.

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Conflict of Interest

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