Chemotherapy Treatment Considerations in Metastatic Breast Cancer

KIROLLOS HANNA,[1] PharmD, BCPS, BCOP, and KELLEY MAYDEN,[2] MSN, FNP, AOCNP®

From [1]Mayo Clinic and M Health Fairview, Rochester, Minnesota; [2]Ballad Health Cancer Care-Bristol, Bristol, Tennessee

Authors' disclosures of conflicts of interest are found at the end of this article.

Correspondence to: Kirollos Hanna, PharmD, BCPS, BCOP, 200 First St. SW, Rochester, MN 55905. E-mail: kirollos11@gmail.com

https://doi.org/10.6004/jadpro.2021.12.2.11

Abstract

Historically, metastatic breast cancer (MBC) was primarily treated with surgery and chemotherapy. To that end, a wide array of chemotherapy agents are currently available for the treatment of MBC. To date, there has been considerable progress in the understanding of the molecular underpinnings of breast cancer, which has led to the development of targeted agents. Despite this, eventually all patients with metastatic disease will receive single-agent or combination chemotherapy either to control spread or as a palliative measure. Currently, combinations of targeted agents and chemotherapy are under investigation, thereby indicating that chemotherapeutic agents will continue to be the backbone of future breast cancer therapy. However, there remains an unmet need to optimize the sequencing of chemotherapy agents based on individual patient characteristics and gene expression profiles in order to reduce toxicities and improve outcomes for patients.

Until the first half of the 20th century, breast cancer was treated mostly with surgical methods (Ades et al., 2017). The correlation between sexual hormones and breast cancer was elucidated in 1967, which led to the development of estrogen-modulating drugs (O'Malley & Khan, 2013). This coincided with the introduction of mustard gas derivatives followed by the recognition of the role of cytotoxic drugs in improving outcomes for patients with breast cancer (Goodman et al., 1984). In 1975, Dr. Gianni Bonadonna, an oncologist from Italy, reported on the efficacy of cyclophosphamide, methotrexate, and fluorouracil (CMF) administered in 1-month cycles for 12 months as adjuvant treatment for node-positive breast cancer (Ribatti, 2007). Similarly, Dr. Bernard Fisher provided evidence supporting the utility of chemotherapy in the adjuvant treatment of breast cancer (Wickerham et al., 2008). Further trials reported that a longer duration (up to 25 years) of the CMF regimen did not result in better outcomes and also identified the safety and efficacy of the inclusion of a noncross-resistant agent such as doxorubicin in patients with breast cancer and positive nodes (Bonadonna et al., 2005; Curigliano et al., 2016). In ad-

J Adv Pract Oncol 2021;12(suppl 2):6–12

dition, Dr. Bonadonna's group confirmed the superiority of the sequential delivery of doxorubicin as a first treatment for four cycles followed by IV CMF and proposed a vision for adjuvant therapy for solid tumors to address micrometastatic disease (Bonadonna et al., 2004). Dr. Bonadonna's group also initiated the concept of primary systemic treatment, tailoring therapy for different prognostic subsets of patients, and neoadjuvant chemotherapy for locally advanced breast cancer (Bonadonna, 1989).

These studies heralded the introduction of anthracyclines and taxanes in the treatment of breast cancer (Ades et al., 2017). Table 1 presents key milestones in the evolution of neoadjuvant/adjuvant chemotherapy–based regimens in breast cancer treatment (Waks & Winer, 2019). Subsequently, studies confirmed the importance of histological subtyping and led to the use of a combination of treatment modalities in improving outcomes for patients while reducing toxicities and morbidities. This shift in breast cancer treatment was pioneered by Dr. Umberto Veronesi who worked in collaboration with Dr. Bonadonna, and developed protocols for partial breast surgeries followed by radiotherapy, chemotherapy, and tamoxifen, when applicable (Veronesi et al., 1986). This multimodal approach continues to be the foundation of breast cancer treatment and has paved the way for the present era of subtype-based targeted therapy (Ades et al., 2017).

CURRENT PERSPECTIVES ON BREAST CANCER THERAPY

Histologic evaluation of breast cancer and use of microarrays and gene profiling analysis has resulted in the identification of different molecular subtypes of breast cancer with distinct clinical behaviors and therapeutic vulnerabilities (Perou et al., 2000; Sørlie et al., 2001). The three subtypes for treatment stratification are hormone receptor positive/human epidermal growth factor receptor 2 (HER2) negative (treated with endocrine targeted therapy and/or targeted therapy), HER2 positive (treated with HER2-directed therapy), and triple negative (treated with chemotherapy, immunotherapy and/or targeted agents; Waks & Winer, 2019). Table 2 summarizes the general approach for subtype-based therapy for MBC (Waks & Winer, 2019). Briefly, for patients presenting with hormone receptor–positive/HER2-negative MBC, early therapy relies on endocrine therapy either alone or in combination with agents targeting phosphoinositide 3-kinase, mechanistic target of rapamycin, or cyclin-dependent kinase [CDK] 4/6 inhibitors (NCCN, 2020; Waks & Winer, 2019). Chemotherapy is reserved for patients with hormone receptor–positive/HER2-negative MBC either refractory to endocrine

Table 1. Key Milestones in the Evolution of Neoadjuvant/Adjuvant Chemotherapy Regimens in Breast Cancer

Representative milestone year	Chemotherapy combination	Observation
1976	Cyclophosphamide/methotrexate/5-FU (CMF)	12 months of this adjuvant combination chemotherapy was shown to significantly reduce recurrence compared with no chemotherapy.
1990	Doxorubicin/cyclophosphamide × 4 cycles (AC4)	AC4 demonstrated equivalent efficacy to 6 months of CMF.
1998	Doxorubicin/cyclophosphamide followed by paclitaxel (AC-T)	Addition of taxane after AC showed improved outcomes compared with AC alone.
2003	Dose density	Better disease-free survival and overall survival was reported with chemotherapy dosing every 2 weeks vs. every 3 weeks.
2006	Docetaxel/cyclophosphamide × 4 cycles (TC4)	TC4 was shown to be superior to AC4 for disease-free survival and overall survival.
2017	Doxorubicin/cyclophosphamide followed by paclitaxel (TaxAC). TaxAC indicates various anthracycline-plus-taxane–containing regimens.	TaxAC regimens were associated with improved outcomes. TC6 demonstrated noninferiority as compared with various TaxAC regimens.

Note. 5-FU = 5-fluorouracil. Adapted from Waks & Winer (2019).

Table 2. General Approach for Subtype-Based Therapy in MBC

Subtype	General approach	Initial lines of therapy	Later lines of therapy	Notes
Hormone receptor–positive and HER2-negative	Serial endocrine therapy–based regimens until disease is endocrine resistant then transition to single-agent chemotherapy.	Aromatase inhibitor plus CDK4/6 inhibitor. In some patients, CDK4/6 inhibitor may be reserved for second line.	Hormonal and/or targeted therapy. If resistant to multiple lines of hormonal therapy, transition to single-agent chemotherapy.	Premenopausal women with hormone receptor–positive MBC should undergo treatment to achieve medical or surgical menopause.
HER2-positive	HER2-targeted agent combined with chemotherapy, or combined with endocrine therapy if hormone receptor positive.	Taxane + trastuzumab + pertuzumab. Selected patients with hormone receptor-positive/ HER2-positive disease can receive endocrine therapy plus HER2-directed therapy.	HER2-targeted agent plus chemotherapy or endocrine therapy if hormone receptor-positive.	HER2-positive brain metastases are common and may be treated with both local and systemic therapies.
Triple-negative	Single-agent chemotherapy or immunotherapy.	Single-agent chemotherapy with either taxanes, platinum agents, or anthracycline agents. Immunotherapy if PD-L1–positive.	Single-agent chemotherapy with capecitabine, eribulin, vinorelbine, gemcitabine, or olaparib or talazoparib if *BRCA1/2* mutations present.	There is no single recommended first-line chemotherapy regimen. Combination regimens can be used only if there is an urgent need for response.

Note. Adapted from Waks & Winer (2019).

therapy or for patients with extensive symptomatic visceral involvement (Schneeweiss et al., 2015). For patients with HER2-positive MBC, HER2-directed therapy is suggested as first- and later-line treatment either in combination with chemotherapy or with endocrine therapy if the tumor is found to be hormone receptor positive.

For patients with triple-negative MBC, single-agent chemotherapy is generally used as initial therapy, but combination chemotherapy is suggested for rapidly progressive visceral disease. For triple-negative MBC patients presenting with germline mutations in breast cancer susceptibility gene 1/2 who have previously received chemotherapy, oral inhibitors of the poly(ADP-ribose) polymerase can be suggested. For patients with triple-negative MBC with tumor expression of programmed cell death ligand 1, the addition of an immune checkpoint inhibitor to chemotherapy (atezolizumab in combination with nanoparticle albumin-bound-paclitaxel [nab-paclitaxel] or pembrolizumab plus chemotherapy) rather than chemotherapy alone is recommended (NCCN, 2020; Waks & Winer, 2019).

Although targeted agents and endocrine therapy have led to significant improvements in progression-free survival, most patients with MBC are known to develop disease progression and/or therapeutic resistance (Early Breast Cancer Trialists' Collaborative Group, 2005). Consequently, most patients with MBC will require cytotoxic chemotherapy either as a single agent or a combination regimen (NCCN, 2020). Chemotherapy is also the treatment of choice in MBC among patients presenting with a large tumor burden involving visceral organs and threatening organ function, regardless of molecular marker expression (NCCN, 2020). Currently, several chemotherapeutic agents are used as monotherapy or in combination with others for MBC (Table 3; Abotaleb et al., 2018; Hernandez-Aya & Ma, 2016; Schneeweiss et al., 2015; Schwartz, 2009). The most commonly used single-agent cytotoxic drug classes include taxanes (docetaxel, paclitaxel, nab-paclitaxel), anthracyclines (doxorubicin, epirubicin, pegylated liposomal doxorubicin), and capecitabine (Abotaleb et al., 2018; Hernandez-Aya & Ma, 2016).

Taxanes are the most frequently used chemotherapy agents in MBC. While both docetaxel and paclitaxel require steroid pretreatment to reduce fluid retention or allergic reactions, nab-paclitaxel has a lower risk of allergic reactions and does not

Table 3. Select Chemotherapy Drug Regimens

Agent/Regimen	Administration route	Dose schedule	Toxic effects
Doxorubicin	IV infusion over 1 hour. Premedication with dexamethasone.	Every 3 weeks (80–100 mg/m^2) or weekly (30–40 mg/m^2) for 3 weeks followed by 1 week off	Cardiotoxicity, myelosuppression, hypersensitivity, extravasation
Paclitaxel	IV infusion over 1, 3, or 24 hours. Premedication with dexamethasone.	Weekly (80 to 100 mg/m^2 on days 1, 8, and 15 of a 28-day cycle) or every 3 weeks (175 mg/m^2)	Neuropathy, myelosuppression, hypersensitivity, extravasation
Nanoparticle albumin-bound paclitaxel	IV infusion over 30 minutes	260 mg/m^2 every 3 weeks	Benefit to patients who are at risk for hyperglycemia and those who cannot tolerate steroids
Capecitabine	Oral	1,000 to 1,250 mg/m^2 twice daily for 14 days followed by 7 days of rest	Edema, fatigue, diarrhea, hypersensitivity, cardiotoxicity
Doxorubicin plus cyclophosphamide	IV	Doxorubicin (60 mg/m^2 IV) over 15 to 60 minutes. Cyclophosphamide (600 mg/m^2 IV) over 30 to 60 minutes. 21-day cycle. 4 cycles in adjuvant setting.	Myelotoxicity, cardiotoxicity, hepatic or renal dysfunction
Sequential fluorouracil, epirubicin, and cyclophosphamide (FEC) followed by weekly paclitaxel	IV	Cycles 1 through 4: fluorouracil (600 mg/m^2 IV); epirubicin (90 mg/m^2 IV); cyclophosphamide (600 mg/m^2 IV). Cycles 5 through 12: paclitaxel (100 mg/m^2 IV) weekly for 8 weeks.	Myelotoxicity, gastrointestinal toxicity, neurotoxicity, cardiotoxicity
Gemcitabine plus paclitaxel	IV	Gemcitabine (1,250 mg/m^2) on days 1 and 8 plus paclitaxel (175 mg/m^2) on day 1 every 21 days	Neutropenia, fatigue, neuropathy
Atezolizumab plus nanoparticle albumin-bound paclitaxel	IV	Atezolizumab (840 mg IV) infusion over 30–60 minutes for days 1 and 15. Nab-paclitaxel (100 mg/m^2 IV) over 30 minutes for days 1, 8, and 15.	Myelotoxicity, peripheral neuropathy, hepatotoxicity, immune-related adverse events

Note. Information from Hernandez-Aya & Ma (2016).

require steroid administration. Anthracyclines are limited to chemotherapy-naive patients with MBC since they are generally employed in the adjuvant setting (Hernandez-Aya & Ma, 2016). Oral capecitabine is usually used as a first-line treatment for MBC patients with bone-predominant, estrogen receptor–positive metastatic disease who have progressed despite at least two trials of endocrine therapy, at least one of which was in combination with a CDK4/6 inhibitor (Hernandez-Aya & Ma, 2016). Other drugs such as eribulin, vinorelbine, gemcitabine, ixabepilone, etoposide, and platinum agents (carboplatin, cisplatin) can be used as front-line therapy among patients with MBC who are not eligible to receive either taxanes, anthracyclines, or capecitabine (Hernandez-Aya & Ma, 2016).

A combination of chemotherapy agents is employed only in the context of a rapidly progressing disease burden resulting in organ dysfunction, when a higher chance of response is imperative regardless of toxicity (Schneeweiss et al., 2015). The most commonly used regimen is an anthracycline plus taxane combination such as doxorubicin plus paclitaxel/docetaxel or doxorubicin, docetaxel, plus cyclophosphamide. Anthracycline-based nontaxane combinations, nonanthracycline, taxane-based regimens, and chemotherapy-immunotherapy regimens are also available. For patients who are not eligible to receive anthracyclines or taxanes, and those who have progressed despite prior treatment, alternative options include ixabepilone plus capecitabine, CMF, and combination regimens incorporating platinum salts

(carboplatin or cisplatin with vinorelbine or gemcitabine; Schneeweiss et al., 2015). Thus, in light of the availability of various therapies and chemotherapy drugs for current clinical practice, the difficulty lies in deciding the optimal sequence of therapy for individual patients with MBC.

TREATMENT CONSIDERATIONS IN METASTATIC BREAST CANCER

The latest National Comprehensive Cancer Network (NCCN) guidelines recommend an individualized approach to MBC management that considers tumor burden, general health status of the patient, preferences, prior treatment, and toxicities (NCCN, 2020). The guidelines also note that currently available systemic treatments for MBC are not curative and encourage participation in well-designed clinical trials (NCCN, 2020). The comparative efficacy and safety profile of therapies is a critical factor for both clinicians and patients. In addition, the tumor burden determines the choice between a single-agent and combination therapy (Waks & Winer, 2019). For example, sequential use of single-agent chemotherapy, which is generally less toxic and has similar outcomes as combination regimens, is preferred for patients with a limited tumor burden and/or minimal cancer-related symptoms (Waks & Winer, 2019). Previous therapy needs to be considered before making treatment decisions since patients who were administered either doxorubicin or epirubicin in the adjuvant setting are candidates for taxanes, but not for repeat anthracycline therapy due to the increasing risk of cardiac toxicity at higher cumulative doses (NCCN, 2020). Microtubulin-directed agents (paclitaxel) should be avoided in patients with neuropathy. Similarly, a history of myelosuppression with prior treatment contraindicates the use of combination regimens, and patients with a history of myelosuppression should instead be prescribed a single-agent anthracycline, capecitabine, or taxane (NCCN, 2020).

Patient preferences and needs are a crucial part of clinical decision-making. While some patients are averse to toxicity risks and would prefer single-agent chemotherapy, others may opt for combination chemotherapy to have a higher chance of response. Some patients have inhibitions regarding alopecia and could be offered agents associated with a lower risk of alopecia, such as gemcitabine (up to 15%), capecitabine (< 10%), and pegylated liposomal doxorubicin (< 20%; Hernandez-Aya & Ma, 2016). Certain patients would prefer IV treatment administered every 3 weeks over weekly schedules and hence would be candidates for single-agent taxanes, anthracyclines, or ixabepilone, or combination therapy using CMF or doxorubicin plus cyclophosphamide (Eek et al., 2016). Others have a strong preference for oral agents, which would limit their options to oral capecitabine (Eek et al., 2016). This is especially relevant during the coronavirus disease 19 (COVID-19) pandemic. Providers need to consider balancing risk for possible exposure to COVID-19 during IV treatments and identify therapies conducive to integration of telemedicine while minimizing the negative impact of social distancing during care delivery. Cost of therapy and reimbursements also need to be factored into shared decision-making to ensure that patient concerns are addressed (Eek et al., 2016). Overall, MBC treatment paradigms need to be optimized for diverse patients and should be adapted to their individual needs.

THE FUTURE OF BREAST CANCER THERAPY

Presently, personalization of breast cancer therapy sequence continues to rely on molecular subtypes determined by hormone receptor positivity/negativity, HER2 positivity/negativity, and triple negativity (NCCN, 2020). However, as mentioned in the previous section, after disease progression or development of resistance, therapy is generally decided based on physical and physiological characteristics of patients (Hernandez-Aya & Ma, 2016). There is therefore an unmet need to further refine existing classifications and inform sequencing of therapy within each broad subtype. The utility of multigene assays in providing prognostic information such as predicting sensitivity to different combinations of agents, determining response to therapy, assessing minimal residual disease, predicting locoregional recurrence, etc., is under investigation (Michiels et al., 2016). Another promising tool for the study of tailoring therapy is the use of patient-derived tumor xenografts or tumor avatar models (Sia et al., 2015). The presence of circulating tumor cells was previously

shown to be an independent detrimental prognostic factor for survival among patients with breast cancer, and ongoing studies will validate the clinical translation of this approach in guiding treatment selection and monitoring the effect (Rack et al., 2014; Siravegna et al., 2017).

The ultimate goal for personalized therapy would be to monitor treatment efficacy in real time, which would enable early recognition of futile approaches instead of the current retrospective method (Ades et al., 2017). For these precision medicine efforts to be realized, drug development pathways and clinical trial designs need to be remodeled to move away from grouping heterogeneous patient populations into limited treatment comparison arms (Deluche et al., 2015; Harris, 2018).

In the near future, the next frontier in MBC therapy appears to be combinations of chemotherapy with targeted agents. Among the ongoing 432 clinical trials in MBC in the United States, 242 studies involve a combination treatment, with 117 utilizing chemotherapy. These include 77 evaluating antimitotic agents, 57 involving albumin-bound paclitaxel, 26 with capecitabine, 21 with carboplatin, and 57 with paclitaxel. A search of targeted therapy combination clinical trials showed that out of the 49 listed studies, at least 40 were evaluating a chemotherapy agent (ClinicalTrials, 2021). Taken together, chemotherapeutic agents play a pivotal role in the treatment of MBC, and ongoing clinical trials using targeted agents in combination with these drugs will determine whether this approach will improve efficacy while reducing toxicity.

CONCLUDING REMARKS

The treatment armamentarium for MBC has expanded rapidly, with more than 60 agents available for use. In spite of remarkable progress, almost all patients with MBC will eventually be treated with chemotherapy agents. There is, however, a need to personalize the treatment of MBC using biomarkers that can inform the sequence of targeted and chemotherapeutic drugs while improving the quality of life of patients.

Acknowledgment

Writing assistance was provided by Nirupama Mulherkar, PhD (NM-INK, LLC), whose work was funded by Athenex, Inc.

Disclosure

Dr. Hanna has served as a consultant for AbbVie and Seattle Genetics, on advisory boards for AstraZeneca, Heron Therapeutics, Incyte, Rigel, Sandoz, Taiho Oncology, on the speakers bureaus for AbbVie, Astellas, BeiGene, Bristol Myers Squibb, and Seattle Genetics, and holds stock in CVS Health. Ms. Mayden has served on the speakers bureaus for Amgen, Pfizer, and Puma, and as a consultant for Amgen.

References

Abotaleb, M., Kubatka, P., Caprnda, M., Varghese, E., Zolakova, B., Zubor, P.,...Büsselberg, D. (2018). Chemotherapeutic agents for the treatment of metastatic breast cancer: An update. *Biomedicine & Pharmacotherapy, 101*, 458–477. https://doi.org/10.1016/j.biopha.2018.02.108

Ades, F., Tryfonidis, K., & Zardavas, D. (2017). The past and future of breast cancer treatment-from the papyrus to individualised treatment approaches. *Ecancermedicalscience, 11*, 746–746. https://doi.org/10.3332/ecancer.2017.746

Bonadonna, G. (1989). Karnofsky memorial lecture. Conceptual and practical advances in the management of breast cancer. *Journal of Clinical Oncology, 7*(10), 1380–1397. https://doi.org/10.1200/jco.1989.7.10.1380

Bonadonna, G., Moliterni, A., Zambetti, M., Daidone, M. G., Pilotti, S., Gianni, L., & Valagussa, P. (2005). 30 years' follow up of randomised studies of adjuvant CMF in operable breast cancer: Cohort study. *BMJ, 330*(7485), 217. https://doi.org/10.1136/bmj.38314.622095.8F

Bonadonna, G., Zambetti, M., Moliterni, A., Gianni, L., & Valagussa, P. (2004). Clinical relevance of different sequencing of doxorubicin and cyclophosphamide, methotrexate, and Fluorouracil in operable breast cancer. *Journal of Clinical Oncology, 22*(9), 1614–1620. https://doi.org/10.1200/jco.2004.07.190

ClinicalTrials. (2021). Clinical trials in metastatic breast cancer. www.clinicaltrials.gov.

Curigliano, G., Valagussa, P., Veronesi, U., & Gianni, L. (2016). The influential and inspirational Gianni Bonadonna's life commitment to evidence-based cancer medicine. *Annals of Oncology, 27*(1), 6–8. https://doi.org/10.1093/annonc/mdv565

Deluche, E., Onesti, E., & Andre, F. (2015). Precision medicine for metastatic breast cancer. *American Society of Clinical Oncology Educational Book, 35*, e2–e7. https://doi.org/10.14694/EdBook_AM.2015.35.e2

Early Breast Cancer Trialists' Collaborative Group. (2005). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials. *Lancet, 365*(9472), 1687–1717. https://doi.org/10.1016/s0140-6736(05)66544-0

Eek, D., Krohe, M., Mazar, I., Horsfield, A., Pompilus, F., Friebe, R., & Shields, A. L. (2016). Patient-reported preferences for oral versus intravenous administration for the treatment of cancer: A review of the literature. *Patient Preference and Adherence, 10*, 1609–1621. https://doi.

org/10.2147/ppa.s106629
Goodman, L. S., Wintrobe, M. M., Dameshek, W., Goodman, M. J., Gilman, A., & McLennan, M. T. (1984). Landmark article Sept. 21, 1946: Nitrogen mustard therapy. Use of methyl-bis(beta-chloroethyl)amine hydrochloride and tris(beta-chloroethyl)amine hydrochloride for Hodgkin's disease, lymphosarcoma, leukemia and certain allied and miscellaneous disorders. By Louis S. Goodman, Maxwell M. Wintrobe, William Dameshek, Morton J. Goodman, Alfred Gilman and Margaret T. McLennan. *JAMA, 251*(17), 2255–2261. https://pubmed.ncbi.nlm.nih.gov/6368885/
Harris, E. E. R. (2018). Precision medicine for breast cancer: The paths to truly individualized diagnosis and treatment. *International Journal of Breast Cancer, 2018*, 4809183. https://doi.org/10.1155/2018/4809183
Hernandez-Aya, L. F., & Ma, C. X. (2016). Chemotherapy principles of managing stage IV breast cancer in the United States. *Chinese Clinical Oncology, 5*(3), 13.
Michiels, S., Ternès, N., & Rotolo, F. (2016). Statistical controversies in clinical research: Prognostic gene signatures are not (yet) useful in clinical practice. *Annals of Oncology, 27*(12), 2160–2167. https://doi.org/10.1093/annonc/mdw307
National Comprehensive Cancer Network. (2020). NCCN Clinical Practice Guidelines in Oncology: Invasive Breast Cancer. Version 6.2020.
O'Malley, B. W., & Khan, S. (2013). Elwood V. Jensen (1920-2012): Father of the nuclear receptors. *Proceedings of the National Academy of Sciences of the United States of America, 110*(10), 3707–3708. https://doi.org/10.1073/pnas.1301566110
Perou, C. M., Sørlie, T., Eisen, M. B., van de Rijn, M., Jeffrey, S. S., Rees, C. A.,...Botstein, D. (2000). Molecular portraits of human breast tumours. *Nature, 406*(6797), 747–752. https://doi.org/10.1038/35021093
Rack, B., Schindlbeck, C., Jückstock, J., Andergassen, U., Hepp, P., Zwingers, T.,...Janni, W. (2014). Circulating tumor cells predict survival in early average-to-high risk breast cancer patients. *Journal of the National Cancer Institute, 106*(5). https://doi.org/10.1093/jnci/dju066
Ribatti, D. (2007). The contribution of Gianni Bonadonna to the history of chemotherapy. *Cancer Chemotherapy and Pharmacology, 60*(3), 309–312. https://doi.org/10.1007/s00280-006-0410-7
Schneeweiss, A., Ruckhäberle, E., & Huober, J. (2015). Chemotherapy for metastatic breast cancer - an anachronism in the era of personalised and targeted oncological therapy? *Geburtshilfe und Frauenheilkunde, 75*(6), 574–583. https://doi.org/10.1055/s-0035-1546150
Schwartz, J. (2009). Current combination chemotherapy regimens for metastatic breast cancer. *American Journal of Health-System Pharmacy, 66*(23 Suppl 6), S3–S8. https://doi.org/10.2146/ajhp090438
Sia, D., Moeini, A., Labgaa, I., & Villanueva, A. (2015). The future of patient-derived tumor xenografts in cancer treatment. *Pharmacogenomics, 16*(14), 1671–1683. https://doi.org/10.2217/pgs.15.102
Siravegna, G., Marsoni, S., Siena, S., & Bardelli, A. (2017). Integrating liquid biopsies into the management of cancer. *Nature Reviews Clinical Oncology, 14*(9), 531–548. https://doi.org/10.1038/nrclinonc.2017.14
Sørlie, T., Perou, C. M., Tibshirani, R., Aas, T., Geisler, S., Johnsen, H.,...Børresen-Dale, A. L. (2001). Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. *Proceedings of the National Academy of Sciences of the United States of America, 98*(19), 10869–10874. https://doi.org/10.1073/pnas.191367098
Veronesi, U., Banfi, A., Del Vecchio, M., Saccozzi, R., Clemente, C., Greco, M.,...Zucali, R. (1986). Comparison of Halsted mastectomy with quadrantectomy, axillary dissection, and radiotherapy in early breast cancer: Long-term results. *European Journal of Cancer and Clinical Oncology, 22*(9), 1085–1089. https://doi.org/10.1016/0277-5379(86)90011-8
Waks, A. G., & Winer, E. P. (2019). Breast cancer treatment: A review. *JAMA, 321*(3), 288–300. https://doi.org/10.1001/jama.2018.19323
Wickerham, D. L., O'Connell, M. J., Costantino, J. P., Cronin, W. M., Paik, S., Geyer, C. E., Jr.,...Wolmark, N. (2008). The half century of clinical trials of the National Surgical Adjuvant Breast And Bowel Project. *Seminars in Oncology, 35*(5), 522–529. https://doi.org/10.1053/j.seminoncol.2008.07.005