



DOI: 10.19187/abc.201963120-123

Systemic Therapy in Local Recurrence of Breast Cancer, Report of a Case and Decision Making in MDT Meeting

Melina Deban^a, Rami Younan^a, Danielle Charpentier^b, Louise Yelle^b, Danh Tran-Thanh^c, Erica Patocskai*^a

^a Department of Surgical Oncology, CHUM hospital, University of Montreal, Québec, Montreal, Canada

^b Department of Medical Oncology, CHUM hospital, University of Montreal, Québec, Montreal, Canada

^c Department of Pathology, CHUM hospital, University of Montreal, Québec, Montreal, Canada

ARTICLE INFO

Received:
08 August 2019
Revised:
20 August 2019
Accepted:
28 August 2019

Key words:
Local recurrence,
breast cancer,
systemic therapy,
chemotherapy

ABSTRACT

Background: Locoregional recurrence of breast cancer has significantly decreased over the last decades, particularly due to effective systemic therapy. While there is little controversy regarding local management of locoregional recurrences, in light of previous systemic treatment, additional chemotherapy regimens and their benefit to the patient are still subject to debate in tumors boards.

Case Presentation: A 45-year-old woman was referred to our tertiary care center with a local recurrence of breast cancer 9 years after modified radical mastectomy for a ypT2N2a invasive ductal carcinoma. She received neoadjuvant treatment consisting of FEC-D (5-FU-epirubicin-cyclophosphamide, followed by docetaxel) for hormone receptor positive, HER-2-neu negative cancer in 2009, as well as adjuvant radiotherapy and tamoxifen for 9 years. After R0 resection of the hormone receptor positive, HER-2-neu negative recurrence in 2019, adjuvant therapy with ovarian suppression and an aromatase inhibitor was undertaken. A multigene assay identified a recurrence score at 37 and benefit from chemotherapy > 15%.

Question: What would the ideal chemotherapy regimen consist of for this patient with an R0 resection of late recurrence of breast cancer?

Conclusion: After reviewing history, imaging and pathology, members of the multidisciplinary team recommended treatment with Taxotere and cyclophosphamide (TC) x 4 for our patient.

Introduction

Owing to advancing therapeutic strategies, locoregional recurrence of patients suffering from breast cancer has improved during recent decades. Chemotherapy use has significantly contributed to this decline.^{1,2} Between 1990 to 2011, locoregional recurrence rate dropped from 30% to 15%.¹ Locoregional recurrence is different according to receptor phenotype; luminal tumors are less likely to recur compared with triple-negative tumors.^{3,4}

Response to neoadjuvant chemotherapy, namely achievement of pathologic complete response, is also associated with decreased locoregional recurrence rate.⁵ The recurrence can be symptomatic or detected by physicians at routine follow up

One of the most important issues in the treatment of such a disturbing and worrisome condition is the selection of the best and the most effective therapeutic options. The role of local treatment options especially surgical resection of the breast cancer recurrence has been well known in treatment of locoregional relapse. On the other hand, radiation therapy may be administered according to some parameters e.g. the previous history of radiation, time between the previous radiation therapy and the recurrence and the dosage of irradiation to the breast and chest wall during the primary tumor treatment. While there is little controversy recommending local

* Address for correspondence:

Erica Patocskai, MD
Associate Professor,
Address: CHUM Hospital, 1000 saint Denis St.,
Montreal, H2X 0C1, Canada
Tel: +1 514 890 8000
Email: erica.patocskai.chum@ssss.gouv.qc.ca



treatment of breast cancer local recurrence, recommendation to treat with systemic therapy is a matter of discussion in most tumor boards. There are two main questions in this field; whether the patient benefits from chemotherapy and what are the best therapeutic regimens recommended in this situation.

Case presentation

A 45 year-old woman was referred in April 2019 to our tertiary care center for late local relapse of breast cancer. She was initially diagnosed in 2009 with multicentric grade 1 hormonal receptor positive, HER-2-neu negative breast cancer. Family history was significant for breast cancer at an unknown age in her mother and a genetics consultation didn't reveal a relevant genetic mutation. She had completed neoadjuvant chemotherapy consisting of FEC-D (5-FU-epirubicin-cyclophosphamide, followed by docetaxel) because of significant extent of the disease in the breast. In April 2010, she underwent a left-sided modified radical mastectomy without reconstruction. Pathology confirmed a principal focus of invasive ductal cancer of maximal diameter of 2.4 cm, along with a second focus of maximal diameter of 2.0 cm. Margins were negative and 4 of the 23 lymph nodes examined were positive for disease. Her disease was classified as ypT2N2a. Adjuvant treatment consisted of radiotherapy to the chest wall completed in July 2010 and tamoxifen for a total projected duration of 10 years. Physical examination and annual imaging were not significant until February 2019, when a 6 mm distortion at the mastectomy scar was reported as BIRADS 4 on MRI. An ultrasound performed in March 2019 identified a 4x5 mm hypervascular lesion on Doppler situated deep to the mastectomy scar. The lesion was biopsied and reported as grade 2 invasive ductal carcinoma, ER 10-20%, PR 70%, HER-2-neu negative. A chest/abdomen/pelvis CT scan confirmed the absence of metastases. On bone scan, there were no signs of bone metastasis. In April 2019, a PET scan revealed reactive lymph nodes that were negative for disease on biopsy. At this time, she was referred to our center and resection was planned. She underwent a resection of the recurrence including part of the pectoral muscle on May 24th, 2019. Pathology confirmed a grade 3 invasive ductal cancer of 1.5 cm, ER 1-5% PR 40% HER-2-neu negative. Closest margins were 5 mm. Since the recurrence occurred while the patient was still on tamoxifen, adjuvant treatment options included ovarian suppression with a GnRH agonist and an aromatase inhibitor. The patient's personal preference was bilateral salpingo-oophorectomy, which she underwent in June 2019. The question of further chemotherapy remained. To quantify her benefit from adjuvant chemotherapy treatment, a multigene assay (Oncotype DX) was requested, even though it is not a standard indication. Her recurrence score was 37,

with a recurrence risk at 9 years with only tamoxifen or aromatase inhibitor of 25% and an absolute benefit of chemotherapy > 15%. Of interest, her receptor status was evaluated by Oncotype DX as ER negative, PR positive, Her-2-neu negative. Her case was presented to the tumor board.

Question

Our specific question to the tumor board regarded the appropriate adjuvant chemotherapy regimen in a patient with an R0 resection of a late recurrence of breast cancer, hormone receptor positive, HER-2-neu negative, status post neoadjuvant chemotherapy consisting of FEC-D 10 years ago.

Discussion

Chemotherapy use has substantially contributed to the decrease in locoregional recurrence rate observed over the past decades. In a review of fifty-three randomized controlled trials from 1990 to 2011, chemotherapy's correlation with decreased locoregional recurrence was significantly larger than endocrine therapy ($P=0.49$ vs. $P=0.24$, P for interaction <0.001).¹ Similarly, a review of NSABP adjuvant systemic therapy trials demonstrated a decrease in both distant metastasis and locoregional relapse with systemic treatment.² Increasing use of chemotherapy poses the challenge of deciding whether or not to treat the recurrence with further systemic treatment and if so, with which regimen.

Few studies have examined the question of adjuvant systemic therapy after locoregional recurrence. GBSG-6 and PACS 03/0003 trials both closed early due to low accrual.⁶ One of the earliest trials completed is the Swiss Group for Clinical Cancer Research (SAKK) trial.⁷ Patients with favorable characteristics, namely estrogen-receptor positive, disease-free interval more than 12 months and three or less nodules each less than 3 cm in diameter, were randomized to tamoxifen or observation. Further local relapses were seen more frequently in the observation group and translated in poorer disease-free survival (DFS) compared to the tamoxifen group (hazard ratio (HR) 0.57, 95% CI 0.39-0.84, $P=0.004$). Overall survival (OS) was similar. Interestingly, the impact of tamoxifen on DFS was significant for postmenopausal patients only, while premenopausal patients had similar DFS in both arms of the study.

The International Breast Cancer Study Group (IBCSG) CALOR study is a cornerstone trial addressing the question of adjuvant systemic therapy in isolated locoregional recurrence of breast cancer.⁸ This international multicentric trial randomized 162 patients with completely excised isolated locoregional recurrences to chemotherapy or no chemotherapy. Chemotherapy regimen choice, including anti-HER2 treatment, was left to physician's preference, but four courses of a



multidrug regimen were recommended. Endocrine therapy was provided to patients with estrogen-receptor positive disease. 45% of patients received an Anthracyclin-based regimen, 19% received docetaxel or paclitaxel alone, 15% received Taxane-based chemotherapy and 11% received capecitabine alone. After a median follow-up of 4.9 years, 5-year DFS was 69% with chemotherapy and 57% without (HR 0.59, 95% CI 0.35–0.99, $P=0.046$). Chemotherapy reduced distant and further local failure. Subgroup analysis revealed the DFS difference to be more significant for estrogen-receptor negative disease compared with estrogen receptor positive disease. The hazard ratio for 5-year DFS with versus without chemotherapy for estrogen-receptor negative disease was reported as 0.32 (95% CI 0.14–0.73) compared to 0.94 (95% CI 0.47–1.89) for estrogen-receptor positive disease. 5-year OS was superior for chemotherapy patients (88%) versus those who didn't receive chemotherapy (76%) (HR 0.41, 95% CI 0.19–0.89, $P=0.024$). Multivariable analysis further confirmed that chemotherapy was significantly associated to 5-year DFS (HR 0.49, 95% CI 0.29–0.84, $P=0.0098$).

The final analysis of the CALOR trial was published in 2018.⁹ It reinforced the benefit of chemotherapy for estrogen-receptor negative disease, but not for estrogen-receptor positive disease. Interaction of treatment by estrogen-receptor status was reported as HR 0.26 (95% CI 0.11–0.60) for receptor-negative recurrence versus HR 0.87 (95% CI 0.46–1.64) for receptor-positive recurrence, $P=0.024$. Overall, the observation of DFS events still favored chemotherapy, though marginally statistically insignificant (HR 0.62, 95% CI 0.38–1.02).

Despite the clear benefit of adjuvant systemic treatment for estrogen-receptor negative recurrence, the lack of benefit for estrogen-receptor positive recurrence is not as clear. Estrogen-receptor positive breast cancer can further be classified in luminal A and luminal B according to index of proliferation and molecular profile. As demonstrated by Belkacemi et al., prognosis and recurrence rates differ between the two subtypes.¹⁰ The question of benefit of adjuvant chemotherapy for luminal B disease, as is the case of our patient, is thus still unelucidated.^{9–11} Furthermore, our patient recurred while on tamoxifen. In CALOR's final analysis, it is stated that the efficacy of chemotherapy could not be assessed in patients who recurred with estrogen-receptor positive disease while on endocrine therapy because of the low number of patients in this cohort.⁹

The trials outlined earlier point to the fact that locoregional recurrence should be managed according to the endocrine molecular characteristics of the recurrence. Moreover, discordance in breast cancer subtype between primary and recurrent breast cancer can affect survival and treatment selection.¹² In that context, the use of genomic signatures for future

therapy is of interest.⁶ It is with that thought that an Oncotype DX score on the recurrence specimen was requested for our patient. The absolute benefit of chemotherapy was estimated to be above 15%. Interestingly, there was discordance regarding ER status between the biopsy and excision specimens and Oncotype DX. ER status was 1–5% at our institution, but Oncotype DX reported an ER negative tumor. As discussed during the multidisciplinary meeting, this was attributed to different pathology lab technique. In the case of receptor negative disease on initial pathology, no Oncotype DX would have been requested; the patient would have received chemotherapy. Regardless, a question would have remained: what regimen should we provide?

In CALOR's discussion,⁸ authors mention that choice of chemotherapy in the trial followed certain principles: if patients had previously received cyclophosphamide, methotrexate and fluorouracil or no chemotherapy, they had an Anthracyclin-based regimen; if they previously received anthracyclines, they were given Taxanes; finally, those who received Taxanes got capecitabine. Our patient previously received FEC-D and so, members of the tumor board advised that chemotherapy with possible cardiac toxicity be preferably avoided. A Taxane-based regimen, namely TC x 4, was hence selected by our multidisciplinary team. As for endocrine therapy, our patient will be switched to an aromatase inhibitor.

As Conclusion, the question of adjuvant chemotherapy for breast cancer recurrence is a subject of debate among many multidisciplinary tumor boards. Though recent trials have proven the benefit of systemic treatment for estrogen-receptor negative disease, estrogen-receptor positive subtypes, i.e. luminal A and B, have been less well investigated. In light of patient history, imaging, pathology and genomic analysis of tumor recurrence, members of our multidisciplinary tumor board elected to administer further chemotherapy consisting of TC x 4 to our patient.

Ethical Consideration

The ethics committee from CHUM Hospital was consulted and it was suggested that written or verbal consent be obtained. Verbal consent was obtained from the patient whose case inspired the discussion.

Conflict of Interest

None.

References

1. Bouganim N, Tsvetkova E, Clemons M, Amir E. Evolution of sites of recurrence after early breast cancer over the last 20 years: implications for patient care and future research. *Breast Cancer Res Treat.* 2013;139(2):603–6.
2. Mamounas EP, Tang G, Liu Q. The importance of systemic therapy in minimizing local recurrence



- after breast-conserving surgery: the NSABP experience. *J Surg Oncol.* 2014;110(1):45-50.
3. Lowery AJ, Kell MR, Glynn RW, Kerin MJ, Sweeney KJ. Locoregional recurrence after breast cancer surgery: a systematic review by receptor phenotype. *Breast Cancer Res Treat.* 2012;133(3):831-41.
 4. Huang EH, Tucker SL, Strom EA, McNeese MD, Kuerer HM, et al. Predictors of locoregional recurrence in patients with locally advanced breast cancer treated with neoadjuvant chemotherapy, mastectomy, and radiotherapy. *Int J Radiat Oncol Biol Phys.* 2005;62(2):351-7.
 5. Swisher SK, Vila J, Tucker SL, Bedrosian I, Shaitelman SF, et al. Locoregional Control According to Breast Cancer Subtype and Response to Neoadjuvant Chemotherapy in Breast Cancer Patients Undergoing Breast-conserving Therapy. *Ann Surg Oncol.* 2016;23(3):749-56.
 6. Pivot X. Adjuvant chemotherapy for local relapse breast cancer. *Lancet Oncol.* 2014;15(2):125-6.
 7. Waeber M, Castiglione-Gertsch M, Dietrich D, Thurlimann B, Goldhirsch A, et al. Adjuvant therapy after excision and radiation of isolated postmastectomy locoregional breast cancer recurrence: definitive results of a phase III randomized trial (SAKK 23/82) comparing tamoxifen with observation. *Ann Oncol.* 2003;14(8):1215-21.
 8. Aebi S, Gelber S, Anderson SJ, Lang I, Robidoux A, et al. Chemotherapy for isolated locoregional recurrence of breast cancer (CALOR): a randomised trial. *Lancet Oncol.* 2014;15(2):156-63.
 9. Wapnir IL, Price KN, Anderson SJ, Robidoux A, Martin M, et al. Efficacy of Chemotherapy for ER-Negative and ER-Positive Isolated Locoregional Recurrence of Breast Cancer: Final Analysis of the CALOR Trial. *J Clin Oncol.* 2018;36(11):1073-9.
 10. Belkacemi Y, Hanna NE, Besnard C, Majdoul S, Gligorov J. Local and Regional Breast Cancer Recurrences: Salvage Therapy Options in the New Era of Molecular Subtypes. *Front Oncol.* 2018;8:112.
 11. Altundag K. Adjuvant chemotherapy might show benefit in luminal B breast cancer patients with isolated locoregional recurrence. *J BUON.* 2019;24(1):405-6.
 12. McAnena PF, McGuire A, Ramli A, Curran C, Malone C, et al. Breast cancer subtype discordance: impact on post-recurrence survival and potential treatment options. *BMC Cancer.* 2018;18(1):203.