Practice-Based Strategies:
Triple-negative Breast Cancer Case

Proceedings from Live Audioconferences
I. Welcome and Case Presentation

**Moderator:** Thank you for participating in this CME and CE audio conference, *Practice-Based Strategies for Managing Metastatic Breast Cancer Patients.*

If you’d like to obtain CME or CE credit for this activity, please complete and submit the online evaluation survey. I hope you enjoy the program and now let me turn it over to Dr. Lyndsay Harris.

**Lyndsay Harris, MD:** Hi. I’m Dr. Lyndsay Harris, associate professor of medicine at Yale Cancer Center, Yale School of Medicine in New Haven, Connecticut. I’ll be discussing the case of a woman who presents with triple-negative disease. Through this overview of her presentation, disease course, and treatment, I hope to highlight practical strategies for managing triple-negative breast cancer in clinical practice.

Let’s begin with a review of the patient’s history. This is a 39-year-old premenopausal female with a family history of breast cancer. Her mother, her older sister, and her aunt all have been diagnosed with breast cancer under the age of 50. It’s important to know that when patients, women, have a family history of breast cancer, it’s important to consider screening at an earlier age than the general population. For example, if a patient or unaffected relative has a person in the family with a breast
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cancer history, it's very important that they be tested for the BRCA1 or 2 gene should that family history have women under the age of 50—or a first-degree relative with ovarian cancer. Screening should begin 10 years younger than that recommended for the general population. For example, in this case, this patient began screening at the age of 30, as her youngest first-degree relative was 40.

Now, our patient had her annual screening mammograms, which detected a 3-centimeter density in the left breast. In addition, there were new calcifications noted in the right breast. She underwent an ultrasound-guided core biopsy on the left and also on the right calcifications.

The left side showed a high-grade invasive ductal carcinoma. There was no evidence of lymphatic invasion in the core and the immunohistochemistry showed ER, PR, and HER2-negative. The right breast showed ductal carcinoma in situ with no evidence of invasion.

Because of the young age and family, premenopausal family history, and bilateral breast cancer, this patient was recommended to undergo testing for BRCA1 and 2. The patient was found to be BRCA1 positive. At that time, her surgeon recommended that she consider bilateral modified radical mastectomy. She was also offered the option of bilateral lumpectomies but given the high risk of a second primary, which can approach
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up to 90% lifetime risk in some studies, the patient elected to have bilateral modified radical mastectomy as her option for surgical management.

The left side showed a 2.6-centimeter high-grade invasive ductal carcinoma, and one of the lymph nodes was positive with a macrometastasis on the left. Fourteen additional lymph nodes were removed on full axillary dissection and were negative. The patient was classified as stage 2B based on the left-sided breast cancer. As noted in the core biopsy, the tumor was ER, PR, and HER2-negative. The right breast examination revealed contralateral ductal carcinoma in situ.

The patient then underwent staging with a CT scan and a bone scan. Questions arise as to whether a PET scan should be performed as staging workup for early stage breast cancer. In my practice, I typically use CT and bone scan, as we know that PET scans have a higher sensitivity but a lower specificity and can lead to greater false positive results. This can lead to patient anxiety and discomfort with unnecessary testing.

Both scans were negative for this patient, and it was recommended to her that she undergo adjuvant chemotherapy. Her surgeon and physician, a medical oncologist, discussed her therapy together in multidisciplinary tumor board. It was recommended
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that she undergo dose-dense doxorubicin, cyclophosphamide followed by paclitaxel, which is a 4-month regimen.

This regimen has been widely adopted for node-positive breast cancer due to the studies from the Cancer and Leukemia Group B Cooperative Group. Initially, the AC-T regimen was given every 3 weeks for four treatment cycles for each regimen. However, newer data from CALGB 9741 showed that every 2-week treatment, also known as dose-dense therapy, improves both disease free and overall survival.

The patient also elected to undergo bilateral salpingo-oophorectomy because of her higher risk for ovarian cancer. A patient who is a *BRCA1* carrier can have a risk for ovarian cancer as high as 40%. It may be slightly lower for patients with *BRCA2* cancers but is elevated compared with the general population.

In follow-up, after completing AC-T chemotherapy this patient was recommended to undergo evaluation every 3 months for the first 2 years and every 6 months up to 5 years, then annually thereafter. At each visit, she would undergo a physical exam, history, routine laboratory data, and imaging was done based on symptoms.

Should she have breast tissue, annual mammograms would clearly be recommended; although, because she had bilateral mastectomies, this was not indicated.
II. Staging of Patients with Early Stage Disease

Lyndsay Harris, MD: The staging workup for a patient with early stage breast cancer sometimes seems to vary. And so, what are my recommendations for patients in the early stage setting? What kind of staging do I perform? And does it differ by subtype? In this patient’s case, she underwent a CT chest, abdomen, pelvis, and a bone scan, and the NCCN guidelines do suggest this as an option, although in some settings, it is potentially the most aggressive approach to staging because she has negative lymph nodes. But because this patient is really more considered higher risk node-negative, in particular because of the high-grade triple-negative breast cancer diagnosis, and because we are planning to give her an aggressive therapy with dose-dense AC-T, I think it’s reasonable to consider CT chest, abdomen, pelvis, and a bone scan.

The recommendations, however, do offer the option of doing a chest x-ray alone and laboratory evaluation, including a CBC and a chemistry panel with liver function test for node-negative breast cancer patients. For node-positive patients, CT chest, abdomen, and pelvis, and a bone scan can be performed. In some settings, greater than four lymph nodes are recommended for the addition of the CT scan.
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Now PET scans have been used more in the recent past, and, in fact, can be reimbursed by many insurance companies, although not all companies will reimburse them for the adjuvant-staging setting. There is concern that’s been raised by clinical trials that there’s a much higher rate of false positives, and given the low frequency of metastases found on CAT scan in patients at low risk of this in the node-negative setting, it is reasonable to do a CT chest, abdomen, pelvis, and a bone scan when that is indicated. Indeed PET scans can be used, but in my own practice usually I reserve those to when there’s a questionable finding on a CT scan or a bone scan.

III. PARP Inhibitors in Triple-Negative Disease

Lyndsay Harris, MD: So our patient was being followed every 3 months as noted above. Those are NCCN guidelines that are recommended for following patients with early stage breast cancer. Of note, there are no standard scans recommended in following breast cancer patients, and tumor markers are also not recommended as two clinical trials performed in the ‘80s and ‘90s showed that there was no survival advantage with the use of tumor markers.

The patient presented at one of her visits with an elevated liver function test, and an imaging CT scan was performed which showed liver metastases. She underwent a
liver-guided biopsy, which was tested for ER, PR, and HER2, as well as standard histology. This showed adenocarcinoma consistent with breast primary and the tumor was again ER, PR, and HER2-negative.

The patient was offered both a clinical trial and standard therapy at this time, and she elected to enroll in a phase III clinical trial of gemcitabine/carboplatin, with or without iniparib, a PARP inhibitor being tested at that time in the phase III setting. She was randomized to the gemcitabine/carboplatin arm and went on to that particular therapy, which lasted for roughly 3 months, at which point she developed progression of disease on restaging CAT scan as well as a rising CA 27-29. As part of the clinical trial, she was offered crossover to the iniparib, which she elected to continue with and had a partial response of 6 months’ duration.

The PARP inhibitors are a very exciting class of drug as they have been shown to have activity in BRCA1 and 2 carriers. PARP inhibitors work by inhibiting single-strand break repair. It is believed that because BRCA1 and 2 breast cancers have a defect in double-strand break repair that combining a single-strand break repair inhibitor in a BRCA1 tumor with chemotherapy will lead to increased cell death. This has been shown in preclinical models and has now been reported in invasive breast cancers from
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BRCA1 and 2 carriers. A very exciting response rate in the preoperative setting has been noted in excess of 60% pathologic complete response.

The patient unfortunately developed progressive disease after having a partial response with the PARP inhibitor, iniparib and chemotherapy, gemcitabine and carboplatin. She was then offered paclitaxel and bevacizumab, which was approved by her insurance company. She received paclitaxel and bevacizumab for over 8 months, at which time she progressed in the liver and also developed CNS metastases. Unfortunately, despite cranial radiation, the patient had a fairly quick decline with liver failure and CNS morbidity, and she passed very shortly thereafter.

IV. Role of Published Guidelines and Clinical Trials

Lyndsay Harris, MD: The NCCN guidelines are broad with multiple potential choices within the metastatic setting. There are first-, second-, and third-line choices and subsequent therapies are often given after third-line, depending on the initial response to treatment. Triple-negative breast cancer is quite chemo-sensitive in many cases, although not all cases. Offering a clinical trial should always be standard of care for metastatic breast cancer and particularly in patients with triple-negative disease as
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this has been shown to be one of the most aggressive types of breast cancer.

Unfortunately, despite chemotherapy and biologic treatment, this patient succumbed after less than 2 years. This is not uncommon with triple-negative disease, which recurs.

It is important to indicate that NCCN guidelines don’t always indicate therapies based on the FDA or product insert.

The patient was offered paclitaxel and bevacizumab as second-line treatment in this case as she had never had the biologic in the past. Of interest, the recent FDA recommendation from ODAC is to withdraw the indication of bevacizumab. However, the FDA has not yet ruled on this. In the meantime clinical trials are ongoing, all of which include the use of bevacizumab both in the metastatic and adjuvant setting. And we are continuing to accrue to those trials and continuing to recommend them. The other thing to keep in mind is that both the NCCN and Medicare have maintained their endorsement of the use of bevacizumab in the metastatic setting. It is, therefore I think, reasonable to offer this therapy to patients who meet the appropriate criteria.

It’s important to recognize that patients with triple-negative breast cancer have specific reasons for choice of therapy in the metastatic setting. The platinums have been shown to be active in this type of breast cancer, although it is yet unclear whether other chemotherapies are less active and remains a question for clinical trials.
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As noted before, we should always consider clinical trials in the setting of an aggressive type of breast cancer, and these were offered to the patient as noted.

V. Question & Answer

Lyndsay Harris, MD: At this point, I’d be happy to stop for any questions from the audience, and please feel free to ask questions regarding this particular presentation or other questions that have arisen about triple-negative disease.

Question 1: Role of repeat biopsy

Lyndsay Harris, MD: A question that arises very commonly is whether or not it’s necessary to repeat a biopsy in a patient where you suspect metastatic disease. It turns out that the past recommendations may be changing with new understanding of disease biology. In particular we know that certain breast cancers may change their markers. Now estrogen-positive breast cancers do not appear to change their subtype completely but may become less responsive to hormonal therapy.

In addition, there are cases of HER2-positive cells recurring, and these are what appears to be present at the time of recurrence. It has not been seen that triple-negative
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breast cancer changes to a different subtype. However, particularly in the case of a patient who’s at high risk for a second breast cancer, one must always keep in mind the possibility of an occult primary which leads to metastatic disease at a later time.

**Question 2: Selecting second- and third-line regimens**

**Moderator:** Dr. Harris, we do have a question. Caller, your line is live.

**Female Speaker:** Yes, Dr. Harris, you talked earlier about reasonable standard chemotherapy regimens for triple-negative disease. When subsequent regimens are needed, how do you then decide what to give in what order?

**Lyndsay Harris, MD:** Sure, that’s a great question, and I think there are many available chemotherapy regimens for breast cancer so we really have a large range of possibilities. The taxanes are typically recommended for first-line treatment; however, in a patient who has already received paclitaxel, I would typically consider an alternative, such as a nab-paclitaxel or docetaxel. If they’re being given in the context of bevacizumab, however, we know that patients do respond, even when they’ve previously had paclitaxel, so I think it’s reasonable to use paclitaxel and bevacizumab, even in a patient who’s received paclitaxel as adjuvant therapy.
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For second and third line, however, there are multiple possible regimens, including single-agent capecitabine, single-agent vinorelbine, single-agent gemcitabine. There’s recently approved regimen with a drug known as eribulin. So all of these different single agents are available to patients.

My own practice is to consider the different side-effect profile of the medications and also the patient’s current circumstances. For example, if a patient is not as compliant, and you have concerns about their maintenance on the therapy, then considering an intravenous therapy may make more sense. On the other hand, a patient who prefers not to come in very frequently and potentially has fear of needles, you would consider a drug like capecitabine, which is an oral formulation of 5-FU for that patient.

Of course, toxicity also is an important consideration, and patients who have considerable neuropathy, either due to prior treatment or due to say diabetes or some other illness, may be less considered for those medications, which cause neuropathy. Vinorelbine, the vincas, and the taxanes all are more associated with neuropathy, and therefore they might be less favored, over things like capecitabine or even eribulin.

There are a number of different choices, and I think one really has to consider the specific information and preferences from the patient, as well as their own medical condition, and take those all into account when making your decision.
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**Question 3: Role of Vitamin D**

**Moderator:** Doctor, we do have another question. It comes from the line of Orlando, Florida. Please go ahead.

**Female Speaker:** Hi, yes, Dr. Harris, can you comment on the use of vitamin D post-adjuvant chemotherapy in this type of patient to try and help prevent recurrence?

**Lyndsay Harris, MD:** Sure, vitamin D has received a lot of press in the last few years, because of the publication showing that lower levels of vitamin D were associated with a higher risk of breast cancer, and there are some small studies suggesting there might be benefit of using vitamin D. However, I think that we have to be very cautious about interpreting those data, as they were not prospective trials. In addition, we know that the recent IOM report suggests that there may be adverse effects from using doses of vitamin D beyond 800 units a day in younger women under 70. Therefore, until we have more definitive data for the use of vitamin D post-adjuvant therapy, I think we should stick to the guidelines for the use of vitamin D to maintain bone density.

**Female Speaker:** Thank you.

**Lyndsay Harris, MD:** You're welcome.
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**Question 4: Use of platinums in triple-negative disease**

**Moderator:** Doctor, we do have another question. Go ahead.

**Male Speaker:** Yes, please. About the choice of adjuvant therapy, being triple-negative, why didn’t you go for platinum combinations?

**Lyndsay N. Harris, MD:** Right. So that’s a very good question. The question that’s being asked by the audience here is whether a platinum should be chosen for adjuvant therapy. Now, there is a fair amount of data now suggesting that triple-negative breast cancer patients may benefit from platinum in—and particularly both cisplatin and carboplatin have been tested in a number of different clinical trials. Specifically for triple-negative breast cancer, Dr. Garber presented a study in the preoperative setting using cisplatin. And in that study they showed that there was a 20-percent pathologic complete response rate with cisplatin alone. It’s important to keep in mind, however, that that was not a randomized trial. And at the current time, there are very few data that compare platinum-containing regimens with standard of care such as the other alkylator-based regimens.

Now, there are studies, for example, from Miami by Dr. Hurley and her colleagues showing that both carboplatin and cisplatin are beneficial in triple-negative
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breast cancer patients. But again, these are phase II studies and don’t compare to standard treatment. There was actually a presentation at ASCO this year looking at standard alkylator-based therapy compared with platinum-based therapy and the addition of the platinum to standard of care, and there was no added benefit to using the platinum in triple-negative breast cancer.

So the other thing to keep in mind is that there are biomarker studies that have looked at sensitivity of triple-negative breast cancer through different types of treatment. And, indeed, Dr. Hayes presented data in *The New England Journal* a few years ago showing that even the taxanes added benefit to standard AC preferentially for the ER-negative including the triple-negative patients.

So in this setting because there are no good randomized trials with platinum-containing regimens in the adjuvant setting for triple-negative breast cancer, I personally feel that standard of care remains the use of either an anthracycline-containing, taxane-containing regimen, or a clinical trial.

**Male Speaker:** Thank you.

**Question 5: Erlotinib in triple-negative disease**

**Moderator:** Doctor, we do have another question. Please go ahead.
Female Speaker: Hi. I’m wondering what you think of the use of erlotinib, the EGFR inhibitor, as an option for triple-negative breast cancer. I noticed that there are a couple of trials underway with erlotinib. I think there’s one in combination with chemotherapy and the other in combination with metformin.

Lyndsay N. Harris, MD: Are you talking about the EGFR inhibitor?

Female Speaker: Yes.

Lyndsay N. Harris, MD: OK, I think in the metastatic setting, there have been several trials looking at the use of the EGFR inhibitors, and one completed by Lisa Carey looked at carboplatin with or without cetuximab. I’m sorry. It was actually cetuximab with or without carboplatin, and there was a small response rate. A low response rate in the order of about 3% or 4%, I believe, for the cetuximab alone, and the combination was quite a bit superior to that.

There does appear to be some activity of the EGFR inhibitors. And there are now ongoing trials looking at carboplatin or cisplatin plus or minus EGFR inhibitors. Because of that fairly low single-agent response rate in Lisa Carey’s trial, I think it is a little bit early to consider that the EGFR inhibitors as likely to be beneficial in triple-negative breast cancer. It still requires further study, I think. And at this point, I think it’s certainly
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a hopeful situation, because we know that the EGFR receptor is overexpressed in as many as 30% of triple-negative breast cancer. But, as with many other targeted therapies, the clinical trials that prove their efficacy over standard chemotherapy would be essential to adopting that treatment.

Female Speaker: Thank you.

Lyndsay N. Harris, MD: You’re welcome.

Question 6: Randomization to the comparative conventional arm in clinical trials

Moderator: Doctor, we do have another question from the line of Middletown, Connecticut. Please go ahead.

Female Speaker: Thank you, Dr. Harris. As you point out, there was enormous interest among patients in enrolling in the iniparib trial, precisely because they had failed other more conventional therapies. But how do you handle with them the fact that they may be randomized to the placebo, or as is in this case, the comparative conventional arm?

Lyndsay N. Harris, MD: That’s a great question, and I think in clinical trials, in general, when there’s an arm that is standard of care versus the arm with the additional
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experimental drug, that’s always an important discussion with the patient so they’re completely clear on their decision. Now in the majority of phase III trials, the comparator is standard of care, and as this combination had been used in the previous phase II trial, and many docs have now started using it, it would be a very reasonable option to offer patients in the metastatic setting with triple-negative breast cancer.

In addition, in this study, patients were offered the opportunity to cross over. In other words, to receive the treatment that is the experimental treatment of iniparib if they progress on the carboplatin and gemcitabine combination. And this patient actually was offered that and did continue to respond for 6 months’ time. It is typically the case in clinical trials that patients are staged somewhat earlier than they would otherwise be on standard of care. So on this trial, patients were staged after two cycles. So it is quite unlikely that anything would occur that would make it difficult for the patient to receive and benefit from subsequent therapy. Did that answer the question?

Female Speaker: Yes. Thank you very much.

Lyndsay N. Harris, MD: You’re welcome.
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**Question 7: PARP mechanism of action**

**Moderator:** Thank you. Our next question is from Dana Point, California. Please go ahead.

**Male Speaker:** Thank you. Just a comment about the use of bevacizumab before I ask you my question. I would just define its use in metastatic disease, but in adjuvant because of its side effects I think that will be too much. My question to you: I'm not clear about the difference of PARP effect on BRCA carriers and triple-negative in general. Could you enlighten us with that?

**Lyndsay N. Harris, MD:** Certainly. I do understand your concern about the use of bevacizumab in the adjuvant setting. And it certainly is not approved for that use and only in the setting of a clinical trial do I think it would be appropriate to consider its use, and only if there’s evidence of overall survival advantage would it be ultimately, I think, approved.

So in the case of the iniparib and the PARP inhibitors, the way that those work, it is believed, is that BRCA1 and 2 are both important in allowing cells to repair their DNA. And specifically, they’re important in double-strand DNA repair. And PARP is an enzyme that’s important in single-strand DNA repair. So the theory goes, and this is...
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backed up by preclinical or in vitro data, is when a cell is vulnerable to double-strand breaks, and you knock out the single-strand break repair mechanism, then the cell no longer has either single-strand or double-strand break repair activity and any sort of DNA damage will cause cell death. This is, some people call it the double whammy, but the bottom line is that you’ve knocked out two important mechanisms of DNA repair for these cells that are already fairly unstable from the genomic perspective, and therefore if any sort of an insult, whether it be just day-to-day cell growth or DNA damage from chemotherapy, it cannot be repaired due to the lack of both single-strand break repair because of the PARP inhibition, and double-strand break repair because of the BRCA deficiency.

Male Speaker: Thank you.

Lyndsay N. Harris, MD: You’re welcome.

VI. Conclusion

Moderator: Doctor, there are no further questions in the queue at this time. Would you like to make any closing comments?
Lyndsay Harris, MD: In closing, I would simply say that the situation of a patient with triple-negative breast cancer really presents a challenge, and we are fortunate in that the evidence thus far suggests that these patients are likely to benefit from chemotherapy. In fact, they are more likely to benefit from chemotherapy than some of the other subtypes, such as the estrogen-positive tumors. However, there are still a subset of triple-negative breast cancer that has recurrence despite the use of chemotherapy, and those patients present the greatest challenge. I think the opportunity for a patient to enroll in a clinical trial is always of priority for these women, and it’s critical to think of new therapies whenever available to potentially overcome resistance to treatment.

Thank you for your attention.

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