Overview

- Is rebiopsy necessary at the time of recurrence or progression of disease?
- How does a very aggressive treatment upfront compare to adopting a longer term treatment strategy?
- How should metastatic disease be monitored?
- What are the most appropriate treatment choices in 2011?
Case 1 – Is another biopsy really necessary?

- AB is a 50 year old woman who had stage II receptor positive Her2 negative breast cancer diagnosed 8 years ago treated with surgery, chemotherapy, radiation and tamoxifen for 5 years.
- She developed a persistent cough. A chest x-ray was abnormal. CT and bone scan showed several lung nodules.
Discordance in receptor status at time of tumor progression

- In 2010, four studies were published on changes in ER/PR/Her2 comparing the primary tumor to metastatic sites. For example, in the one prospective study:
  - ER positive to ER negative – 12%
  - ER negative to ER positive – 14%
  - Her2 negative to Her2 positive – 5%
  - Her2 positive to Her2 negative – 12%
Does breast cancer change with time in a meaningful way?

- Dr. Lisa Carey, UNC, in “2010 Year in Review Metastatic Disease” concluded:
  - These are small but real changes in important markers.
  - Biopsy is recommended at the time of relapse.
    - This allows confirmation of metastatic disease.
    - Rechecking ER/PR/Her2 can provide useful information to guide treatment.
Case 2 – Is very aggressive treatment better?

- CD is a 35 year old woman with newly diagnosed triple negative metastatic breast cancer to bone. She has a close friend who was diagnosed with stage III breast cancer 10 years ago treated with high dose chemotherapy and a bone marrow transplant.
- Why isn’t that same approach recommended now?
High dose chemotherapy for breast cancer (HDC) - “a troubled quest”

- Dr. Donald Berry, an expert breast cancer statistician, recently analyzed 15 adjuvant and 6 metastatic breast cancer trials comparing standard treatment to HDC, reported in JCO, August 2, 2011
- What was the rationale behind this approach and why is it no longer recommended?
High dose chemotherapy for breast cancer

- Some chemotherapy drugs have a steep “dose-response curve.” Very high doses require bone marrow support.
- Positive results in lymphoma spurred interested in breast cancer.
- Early phase II results were promising; a small number of patients became long term survivors.
- Breast cancer quickly became the main indication for bone marrow transplantation.
High dose chemotherapy for breast cancer

- 866 women with metastatic breast cancer enrolled in 6 trials comparing HDC to standard treatment.
  - Although there was a small improvement in “disease-free survival” (11 v. 8 months), there was no difference in overall survival (2.1 v 2.0 years).
  - No subset of patients seemed to benefit.
  - It is unlikely that HDC will ever play an important role in breast cancer.
High dose chemotherapy for breast cancer: Lessons learned

- Major advances in transplant medicine were achieved.
- Treatment related deaths fell from 10% to 1%.
- New areas of research developed, for example CTC’s (circulating tumor cells) in blood and bone marrow.
High dose chemotherapy for breast cancer: Lessons learned

- Patients were chosen based on their physiologic status, not tumor characteristics.
- There was no good link between breast cancer research and transplantation research; both the treatment arms control arms were “far from standard.”
- Insurers were pressured into providing coverage for trial participation which established HDC as a highly reimbursed standard treatment before good clinical data was available.
Advice about very aggressive treatment for metastatic breast cancer

- Data should be collected from two or more large well conducted clinical trials before new treatments are adopted.
- Even when the early results are very promising, some long term data is needed before a change in standard of care.
- Negative findings need to be reported.
- Insurance companies now typically cover clinical trial participation.
- Clinical trial design now requires translational approaches and use of biologic pathways.
Case 3 – How should patients with metastatic disease be monitored?

- EF is a 65 year old woman with receptor negative Her2 positive metastatic breast cancer to liver. She is just starting Xeloda/Capecitabine.
- What type of monitoring should she undergo while she is on this regimen?
Recommendations for monitoring metastatic disease

- There are no standardized guidelines in the US and wide variation in practice.
- ESMO (European Society of Medical Oncology) guidelines were recently updated in September 2011.
  - Response evaluation is recommended after 2-3 months of endocrine therapy and after 2-3 cycles of chemotherapy.
  - Response evaluation includes symptoms, lab tests and repeating the initially abnormal scans with direct comparison.
Recommendations for monitoring metastatic disease

- Serum tumor markers can be helpful in monitoring disease but should not be used as the only determinant for treatment decisions.
- PET-CT scanning is still considered investigational by ESMO and typically not allowable in US cooperative group trials.
- There is no defined optimal visit schedule for patients who are not on active treatment.
- Patients need instructions on symptoms that are suggestive of progressive disease.
Recommendations for monitoring metastatic disease

- Patients need good quality information (a Care Plan) outlining the goals of their treatment with information about possible side effects and the impact on their functional, emotional and social well-being.
  - ASCO (www.asco.org)
  - NCCN (www.nccn.org)
  - ONS (www.ons.org)
Recommendations for monitoring metastatic disease

- Symptom reporting is important.
  - Symptom diaries
  - ASCO iPad app (www.cancer.net)
- Labwork and scans should be done periodically but should not replace symptom assessment.
How should patients with metastatic breast choose treatment?

- GH is a 55 year old woman with newly diagnosed hormone receptor negative Her2 positive metastatic breast cancer to lungs and bone initially detected on a preoperative chest x-ray for knee replacement surgery. She has no other significant medical problems.
- How should she prioritize her treatment options?
Treatment options for metastatic breast cancer - 2011

- There is a growing number of standard therapies.
- There is an increasing number of breast cancer subtypes.
- Survival depends on the biology of the tumor and the tempo of the disease.
- The goal of treatment = to control the disease and its symptoms while maximizing quality of life.
Treatment options for bone metastases

- Aredia/Pamidronate IV and Zometa/Zoledronate IV have been recommended to decrease the likelihood of “skeletal related events.”
- Xgeva/Denosumab (subcutaneous) was recently shown to be modestly more effective at preventing SRE’s than Zoledronate with comparable side effects.
Treatment options for bone metastases

- Adequate calcium and vitamin D are important for effectiveness of drugs in both classes.
- The subcutaneous method of administration is easier than IV.
- Xgeva/Denosumab can be used in patients with renal insufficiency.
- The likelihood of serious adverse events (ONJ) is comparable for both drugs.
Treatment of metastatic Her2 positive breast cancer

- There are four Her2 targeted agents which have been studied as first line monotherapy:
  - Herceptin/Trastuzumab
  - Tykerb/Lapatinib
  - Neratinib
  - TDM-1
Introduction to TDM-1

- TDM-1 combines Her2 targeting with a highly potent chemotherapy drug.
- In one small study, the objective response rates and clinical benefit were higher with TDM-1 than with the combination of Trastuzumab and Docetaxel.
- Serious adverse events were comparable in both groups (13% and 15% respectively).
Are two Her2 targeting drugs better than one?

- In one small study of women with pretreated metastatic breast cancer, progression free survival, overall survival and clinical benefit rate were modestly improved with the combination of Lapatinib and Trastuzumab compared to Lapatinib alone.
- There is also some preliminary supportive evidence in the neoadjuvant setting.
What is the role of anti-angiogenic drugs in metastatic breast cancer?

- Sunitinib + Capecitabine did not improve progression free survival in patients with metastatic breast cancer compared to Capecitabine alone.
- Four trials of Bevacizumab in combination with chemotherapy showed improvement in progression free survival but not overall survival (E2100, AVADO, Ribbon-1 and Ribbon-2)
A new drug for heavily treated metastatic breast cancer – Eribulin

- The EMBRACE trial randomized 762 patients (2:1) to Eribulin vs. treatment of physician’s choice.
- 1-year survival rates were 54% for Eribulin and 44% for TPC.
- Median survival rates were 13 months for Eribulin and 10 months for TPC.
- Eribulin has a very favorable therapeutic window.
PARP Inhibition

- PARP inhibitors alone appear to work in BRCA1/2 associated cancer.
- A phase II study of Iniparib in triple negative breast cancer showed improvement in PFS and OS with very little toxicity, but the phase III study was negative.
- Other PARPi are under investigation.
High priority clinical trials for metastatic breast cancer

- Vaccine trials for Her2 positive metastatic breast cancer with no evidence of disease and for Her2 negative metastatic breast cancer with measurable disease.
- Iniparib and Irinotecan in triple negative breast cancer with brain metastases
- TDM-1 or Herceptin/Trastuzumab with GDC-0941 in metastatic breast cancer
High priority clinical trials in metastatic breast cancer - 2011

- The Stand Up 2 Cancer Study
  - Subcutaneous Azacitidine (a DNA methyltransferase inhibitor) and oral Entinostat (a histone deacetylase inhibitor) in metastatic breast cancer.
- Oral hedgehog (GDC-0449) and oral notch (RO4929097) inhibitors in metastatic breast cancer
High priority clinical trials for metastatic breast cancer - 2011

- **MARIANNE** – first line
  - A 3-arm study of TDM1 + Pertuzumab or Pertuzumab placebo vs. Trastuzumab + a Taxane

- **TH3RESA** – third line
  - A 2-arm study of TDM1 vs. TPC
  - Sunitinib + Gemcitabine + Carboplatin

- [www.triplenegativefoundation.org](http://www.triplenegativefoundation.org)
- [www.cancer.gov](http://www.cancer.gov)
Advice for choosing treatment for newly diagnosed metastatic breast cancer

- There are many standard options to consider (hormone therapy, chemotherapy and biologic therapy).
- Always consider clinical trials participation using a standard agent in combination with one or more new agents.
- Clinical trial participation can be considered as 1\textsuperscript{st}, 2\textsuperscript{nd}, and 3\textsuperscript{rd} line therapy.
References/Resources

- MBCN (www.mbcn.org)
- Foundation for Informed Medical Decision Making (www.informedmedicaldecisions.org)
- ASCO (www.asco.org)
- NCCN (www.nccn.org)
- SABCS (www.sabcs.org)
- www.breastcancer.org