METASTATIC BREAST CANCER: CONTROLLING THE HERD WHEN THE HORSES ARE OUT OF THE BARN

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MITIGATING POTENTIAL BIAS

- Not Applicable

OBJECTIVES:

- List the most common presenting signs of metastatic breast cancer
- Describe the options and sequencing of treatment for metastatic breast cancer
- Explain the difference in treatment recommendations for metastatic:
  - Hormone receptor positive breast cancer (ER +/or PR positive)
  - HER2 positive breast cancer
  - Triple negative breast cancer

TREATMENT RECOMMENDATIONS CAN BE COUNTERINTUITIVE

- Often patients and non oncology trained primary health care or other care providers assume that metastatic disease should be treated more aggressively than non metastatic
- The "horses out of the barn" analogy is meant to highlight why this is not the case
- More aggressive therapy does not result in cure or even in better survival
  - But does result in **more toxicity**

CASE A

- 53 year old female with a past history of infiltrative ductal breast cancer, pT2N0, grade 2, **ER pos, PR pos**, and Her 2 negative 3 years ago
- Treated with chemotherapy (FEC D), adjuvant radiation and started Tamoxifen but stopped after 2 months because of adverse effects with hot flashes
- Presents with back pain for 1 month
- Saw family physician and prescribed Naproxen and Robaxin
- Worsening over past 3 days and now weakness in legs and a fall
- No bladder or bowel symptoms

WORKUP:

- X-ray spine – report – concerning for possible lesion at L1 vertebral body
- MRI back done urgently: soft tissue mass with spinal cord compression at L1 vertebral body and multiple small lytic lesions in the thoracic and lumbar spine vertebral bodies
- Managed with palliative local irradiation and steroids with good control of symptoms
- Bonescan: suspected lytic lesion in pelvis and sternum
- Biopsy of bone not possible
  - Value of rebiopsy?

ER AND PR STATUS IN METASTATIC DISEASE

- Up to 25 % in some studies discordance between the primary tumour and the metastatic lesions
- 20 % change in treatment plan based on results

CASE B:

- 64 year old previously healthy female presenting with new fungating left breast cancer with axillary and cutaneous nodules eroding through the skin in the forearm, with grossly edematous left arm

WORKUP?

- CT chest, abdomen and pelvis – pending
- Bonescan pending
- Pathology: poorly differentiated carcinoma
- ER negative/PR negative
- Her 2 neu positive

- Note: Often start treatment before staging complete for palliation of disease in cases of locally advanced disease
- In this case already know it is metastatic – with cutaneous distant disease in the arm
- CT confirms small bilateral lung nodules 1.2 cm maximum diameter

NEGLECTED BREAST CANCER

- Every year a number of women present with a history of a breast mass that has been neglected and it is very advanced at presentation
- Often difficult to tell how fast the lesion grew to the current size, and often the patient will minimize the length of time from initial breast changes to presentation

CASE C:

- 22 year old female with history of breast cancer detected during pregnancy 1 year ago in right breast, ductal histology, grade 3, ER neg, PR neg and Her 2 neu neg (Triple Negative histology)
- Declined adjuvant chemotherapy for this T2 N0 breast cancer despite recommendations and refused further appointment with CCMB
- Seeing naturopath for past 1 year
- Presented to her family doctor with weight loss, pruritus, early satiety and fatigue

WORKUP:

- Bloodwork: Total bilirubin 120, Direct 100, AST 44, ALT 54, ALK Phos 600, GGT 712
- CT abdomen: inumerable liver metastases and biliary ductal dilatation (intrahepatic) with portal region mass compressing bile duct
- Referred for urgent ERCP and stent placement
- CT chest: new lung lesions in left upper lobe with largest measuring 1.2 cm maximum diameter

MOST COMMON SYMPTOMS OF METASTATIC BREAST CANCER

- Asymptomatic (found incidentally)
- Bony pain or spontaneous (pathologic) fracture
- Neurologic symptoms from spinal cord compression
- Weight loss
- Loss of appetite
- Abdominal pain
- Early satiety
- Fatigue
- Jaundice/pruritis
- Headaches
- Seizures

SYSTEMIC THERAPY OPTIONS

SYSTEMIC THERAPY

- **Important information to guide treatment decisions:**
- Disease and/or biologic factors:
  - Hormone status of tumour (ER/PR)
  - Her 2 neu status of tumour
  - Grade of tumour
  - Sites of disease:
    - bone only vs. visceral disease vs. metastatic to brain
  - Rate of progression of disease
  - Disease burden

- Patient Factors
  - Previous treatment and timing of that treatment
    - If prior adjuvant – time from completion to detection of metastatic disease
  - Menopause status
  - Performance status of the patient
  - Frailty of patient
  - Expectations/preferences of patient

GOALS OF CARE

- Palliative
  - Quality of life
    - Improve symptoms from the cancer (or prevent them)
    - Limit/Control toxicities of the treatment
- Prolongation of Survival

- ***One goal does not supersede the other***

BACK TO CASES:

- **Case A**: 53 year old female with a past history of infiltrative ductal breast cancer, pT2N0, grade 2, ER pos, PR pos, and Her 2 negative 3 years ago, bone only disease
- **Case B**: 64 year old previously healthy female presenting with new fungating left breast cancer, ER neg, PR neg, Her 2 neu pos, cutaneous and pulmonary metastases
- **Case C**: 22 year old female with history of breast cancer, triple negative, visceral metastases

CASE A TREATMENT OPTIONS:

- Hormone receptor positive, Bone only disease and radiation initiated to control the destructive lesion and provide symptom relief
- Little prior endocrine therapy and no recent expposure
- Goals:
  - to palliate and control symptoms while avoiding excess toxicity, and prolong life
- Endocrine therapy vs chemotherapy:
  - No evidence that chemotherapy first line improves survival
  - Without rapidly evolving disease, preferable to use less toxic and more tolerable treatment, but neither is better in terms of overall survival benefit
  - **Endocrine therapy** generally would be used first to minimize toxicities
    - Options for menopausal females: Aromatase inhibitors: letrozole, anastrazole, exemestane
    - Everolimus an option with AI therapy after progression on AI
    - If premenopausal: Tamoxifen or Goserelin with addition in a couple of months of one of the aromatase inhibitors above
    - *Fulvestrant: generally used in second line setting, though new data may change its place in therapy in future

CASE A (CONTINUED)

- What about if she had multiple large liver metastases as well?
  - More compelling to start with chemotherapy and stabilize disease first, then proceed to endocrine therapy when stable.
  - If small burden of visceral disease, still have the option of endocrine therapy first
- If on endocrine therapy when developed metastases?
  - Likely switch to alternate endocrine agent though chemo or endocrine decision may be dependent on sites/burden of disease and performance status and wishes of the patient:
    - If on anastrozole or letrozole, could either switch to exemestane or fulvestrant (PCODR pending)
    - alternately - tamoxifen

CASE A: SEQUENCING OF ENDOCRINE AGENTS

- Generally try to avoid switching therapy with minor progression in a single or few bone regions that can be controlled with radiation
- If multiple sites of progression should consider changing therapy, and if rapid progression, new visceral metastases or very symptomatic may wish to consider chemotherapy to stabilize disease
- Endocrine therapy can be returned to if chemotherapy reduces disease burden and stabilizes disease

ENDOCRINE OPTIONS:

- **After first line:**
  - May consider Fulvestrant 500mg IM (day 1, 15, 29, then every 4 weeks)
  - May also proceed to chemotherapy anywhere in the sequence to improve disease stability and retry endocrine later
- **Options for Chemotherapy:**
  - **Capecitabine – Hormone receptor positive - often more responsive**
  - **Docetaxel or Paclitaxel or Abraxane**
  - **FEC50**
    - **If bone marrow infiltration concerns may need to use less myelosuppressive regimen: Adriamycin weekly**
  - Eribulin
  - Vinorelbine
  - Gemcitabine + Vinorelbine

CASE B:

- With Her 2 neu positive and ER/PR negative disease, the most evidence based treatment in the **first line setting** for palliative and disease control/symptom control is Pertuzumab, Trastuzumab and Docetaxel therapy to start with, then stop docetaxel and continue Pertuzumab and Trastuzumab alone
  - If suitable for this regimen the overall survival advantage is more than 16 months in comparison with docetaxel with trastuzumab alone
  - Substudy analysis – less advantage for the group without visceral metastates, and in HR pos may also consider endocrine agents with trastuzumab alone
  - Not a candidate if metastatic recurrence during adjuvant therapy or within 6 months of completion of adjuvant Trastuzumab containing therapy
- After first line therapy, evidence supports TDM1 (Trastuzumab emtansine) for second line but other potential options include Trastuzumab and other chemotherapy such as capecitabine followed by TDM1

WHAT IF RECURRENT DISEASE AFTER PRIOR TRASTUZUMAB THERAPY (ADJUVANT)?

- Patients enrolled in the trial with Pertuzumab, Trastuzumab and Docetaxel metastatic protocol had to have a minimum of 6 months from last Her 2 directed therapy (adjuvant) prior to diagnosis with metastatic disease
- If progression with metastatic disease seen within 6 months, patients are considered refractory
- Would then have option for:
  - Docetaxel (or Paclitaxel) with trastuzumab or Capecitabine with trastuzumab or
  - Proceed to Traztuzumab emtansine (TDM1)

ON PROGRESSION?

- Other options include:
  - FEC50
  - Capecitabine
  - Vinorelbine
  - Eribulin
  - Cisplatin and gemcitabine
  - Gemcitabine and paclitaxel

- NOTE: If this patient was HR positive?
  - Could have started with endocrine therapy with Trastuzumab if no visceral metastases

CASE C: TREATMENT OPTIONS:

- Non endocrine responsive disease
- No targets to employ
- Chemotherapy is only option:
  - Most common sequence:
    - Start with Docetaxel or Paclitaxel – better overall survival seen with starting with Taxane or anthracycline
    - Anthracycline – FEC50 most common in Canada
    - Capecitabine – less responsive to this drug than the HR positive group, but may consider trial in the third line for tolerability sake
    - Eribulin – (microtubule inhibitor)
    - Vinorelbine
    - Cisplatin & Gemcitabine

OTHER TREATMENT OPTIONS:

- Palliation – patients in Winnipeg do not have opportunity to enroll in Palliative Care Program while on chemotherapy
- Patients in Rural Areas can be enrolled while on treatment, but still should have a 3 – 6 month expected survival maximum – enrolling early in breast cancer likely not necessary or indicated unless very aggressive disease
- Median survival is 2 years at presentation with metastatic disease but range is wide
  - Longest seen generally in bone only metastatic disease

TOXICITY PROFILE:

Drug Family	Line of Therapy	Toxicities
Aromatase Inhibitors (AI) (Anastrazole, Letrozole, Exemestane)	Postmenopausal: First line Premenopausal: Only if on GnRH agonist (generally second line)	Hot flashes Vaginal dryness Aches and pains Decreased bone density Cognitive effects Increased cholesterol
GnRH agonist	Premenopausal: generally second line and add AI after menopausal biochemically	As above
Tamoxifen	Premenopausal: first line Postmenopausal – later line	As above for AI – except increase in bone density likely for postmenopausal patients and less aches and pains Potential for flare of disease before benefit
Fulvestrant	Second line – clear benefit	As above for AI Less aches and pains No flare response

CHEMOTHERAPY:

Protocol or Drug Family	Line of Therapy:	Toxicities:
Taxanes •Docetaxel •Paclitaxel •Albumin bound paclitaxel (abraxane)	First Line or later	Drug reactions/allergic reactions Peripheral neuropathy Peripheral edema Alopecia and nail changes, rashes *Diarrhea *mucositis *myelosuppression *Nausea/vomitting
Anthracyline •EC, FEC50 OR FEC100 •AC, FAC or PLD or adriamycin weekly	First line or later	* + Cardiotoxicity Alopecia Nausea/vomiting
Antimetabolites •Capecitabine •Gem/Carbo •Gem/Paclitaxel	First line or later Later lines Later lines	Diarrhea & Hand and foot syndrome * + alopecia Taxane toxicities, pulmonary (Gem)
Other antimicrotubule: •Vinorelbine •Eribulin	Generally later lines Generally 3rd or 4th	• + Neuropathy – GI most prominent -Nausea & constipation • Fatigue and myelosuppression
Platinum agents with Taxane •Docetaxel + Carbo	Generally later lines	* + Nausea/vomiting Hearing loss neuropathy

BIOLOGIC AGENTS:

Biologic and targeted/Other Agents:	Setting of Use:	Toxicities:
HER2 directed: • Pertuzumab + Trastuzumab + Docetaxel/paclitaxel • Lapatinib + capecitabine	First line only Third line (not funded)	Cardiotoxicity Docetaxel side-effects Fatigue Nausea, vomitting, Diarrhea, fatigue, skin rashes, HFS, myelosuppression
Other regimens: • CMF • Cyclophosphamide • Carboplatin single agent	Not commonly used	myelosuppression fatigue Diarrhea Nausea & vomiting

SUMMARY:

- Many Options for treatment of metastatic breast cancer
- Best option is dependent on multiple factors including biologic features of the tumour, sites of metastatic disease, and patient factors
- Biology of metastatic disease may differ from the original primary tumour
- Sequencing is very individualized and often confusing
- Patients are given options as well as recommendations, and decisions may be based on their preferences based on toxicity profiles and on their performance status

SUMMARY:

- More toxic is not always better:
- Metastatic Disease does not mean that the best option is chemotherapy
- The best treatment is the one that meets the cardinal goals of treatment:
  - Quality of life
    - Palliate symptoms of the cancer
    - Limit the toxicities of the therapy
  - Improve the survival of the patient