Locally advanced breast cancer in the developing countries

Moderator: Prof V.O.L. Karusseit

Dr. Mark D. José
Locally Advanced Breast Cancer Definitions

- LABC that may be operable at presentation:
  - Stage IIIA: T0 - T3 with a N1-2; N2 with any T1-T3
- LABC that is inoperable at presentation:
  - Stage IIIB: T4a, skin; T4b, chest wall; T4c (a1b) with N1-N2.
  - Stage IIIC: N3 with any T, T4d (inflammatory breast cancer)
Introduction

- Currently in South Africa 10% of patients with breast cancer present with stage 1 ds. & the remainder presents with 30% each for stages 2, 3 & 4.
- Whilst between 60%-80% of patients present with LABC & metastatic ds. in low to middle income countries.
- LABC has decreased to 15% in countries with enhanced resources thanks to widespread education and screening programs Canada & the United States.
- LABC and metastatic breast cancer are the most common stages at presentation in most low-resource countries.
Introduction

• Stage at diagnosis, histological grade & aggressiveness of tumour, availability & access to appropriate treatment modalities all play a major role in poor outcome.

• Overall 56% - 5 year mortality in all stages of breast cancer when compared to the U.S. - 88% & S.A.: - 80% whites but black 64%, in a Ugandan study.
Neoadjuvant chemotherapy/primary systemic therapy

- Multidrug chemotx. – EBCTCG-95 & 2000: reduction in disease recurrence & death in node +ve or -ve, regardless of age, receptor status, menopausal status & stage.
- “Sandwich” techniques – neoadjuvant chemotx ffg by postop chemotx. then radiotx.
- Use antracycline based regimen.
- Sequencing chemotx. in relation to surgery does not influence oncologic parameters provided postoperative chemotx. is started within 30 days.
- Preop radiotx influences complication rates- local wound infection 25%, 34% delayed wound healing, 63% seroma formation, 22% lymphoedema rate.
Local recurrence:
• Isolated local–regional recurrence should be treated like a new primary with a curative intent including ‘secondary’ adjuvant treatment modalities as appropriate [II, B].

Locally recurrent or metastatic breast cancer: ESMO – 2009

Reconstruction:
• Immediate vs. Delayed-immediate:
  Prosthesis placed after surgery/ free or pedicled flap done immediately vs. tissue expander after surgery & either prosthesis or tissue flap after radiation
• Delayed- immediate repair had the best outcome with fewer complications: extrusion of prosthesis, distortion of chest wall & limited ability to treat targeted tissues.

2009 Aug;124(2):395-408
Post-operative radiotherapy

• Decreased incidence in locoregional recurrence 11% vs. 26% after 10yrs –proven by NSABP 18 & 27 trials – for stage 2B & 3 ie lymph node +ve

• Neoadjuvant chemotx. with BCT and radiotherapy.

• However controversy in positive margins/close margins in node –ve patient (T3,N0,M0). Truong et al- 4.9% vs 3% for development of locoregional recurrence , Ahlborn et al, Mentzer et al.

• All data are retrospective. Further PRCT with larger number are required.
Role of “toilet” total mastectomy:

- Controversial not mentioned in most current literature.
- Fungating & offensive smelling - for local control to improve quality of life and alleviate social & psychological factors in patients with poor physiological reserve.
- 30% – 40% local recurrence.
- Increased incidence of distant metastasis without systemic therapy.
- Increased rates of wound dehiscence, wound infection, seromas – when associated with preoperative radiotherapy.

• Operable, large tumors are managed by PST at the enhanced and maximal resource levels, they should be managed with primary surgery followed by adjuvant therapy and radiation in countries with basic resources (retrospective studies to support this practice, McCammon et al, Floyd et al & Taghian et al between 7.1% - 10% local recurrence after 10 years)

• PST is recommended for inoperable LABC at all resource levels. PST includes anthracycline-based chemotherapy, preferably sequenced with taxanes

• Tamoxifen remains useful and is recommended for patients with ER-positive tumors in limited resources
Guidelines - developing world

• AIs produce better results than tamoxifen and are recommended for countries with enhanced and maximal resources
• Chemotherapy generally is completed before surgery, and there are no data yet to support additional chemotherapy after surgery
Guidelines - developing world

• Hormone therapy should be used after surgery for at least 5 years.
• Trastuzumab combined with taxanes yields high pathologic response rates in patients with HER-2/neu-overexpressing tumors, it is recommended in countries with enhanced and maximal resources, and it should be made available in countries with lower levels of resources at lower costs.
Guidelines - developing world

• To use PST, countries should have FNAB or core breast biopsy and receptor determination available at presentation, and an adequate pathologic evaluation of response to therapy should be available

• To save costs, determination of ER status without progesterone receptor status is considered adequate
- Guidelines - developing world

- HER-2/neu receptor status is highly desirable; however, the costs of testing and subsequently trastuzumab therapy in HER-2/neu-positive patients remain prohibitive.
- If immunohistochemistry available to detect tumors with HER-2 expression and to offer trastuzumab accordingly.
Guidelines - developing world

• Tumors with HER-2/neu expression determined by immunohistochemistry require fluorescence in situ hybridization for confirmation, and that complementary assay is recommended at least for countries with enhanced and maximal resources.

• Multidisciplinary approach is imperative for the optimal management of LABC and should be developed, with whatever specialists are available.
• **Basic level**—Core resources or fundamental services that are absolutely necessary for any breast healthcare system to function, in a single clinical interaction.
• **Limited level**—services that are intended to produce major improvements in outcome such as increased survival, and are attainable with limited financial means and modest infrastructure, single or multiple clinical interactions.
• **Enhanced level**—services that are optional but important; enhanced-level resources should produce further improvements in outcome and increase the number and quality of therapeutic options and patient choice.
• **Maximal level**—services that may be used in some high-resource countries and/or may be recommended by breast care guidelines that do not adapt to resource constraints but that nonetheless should be considered a lower priority than those resources or services listed in the basic, limited, or enhanced categories.
<table>
<thead>
<tr>
<th>Level of resources</th>
<th>Local-Regional Treatment</th>
<th>Systemic Treatment (Adjuvant or Neoadjuvant)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surgery</td>
<td>Radiation Therapy</td>
</tr>
<tr>
<td>Basic</td>
<td>Modified radical mastectomy</td>
<td>*</td>
</tr>
<tr>
<td>Limited</td>
<td>Postmastectomy irradiation of chest wall and regional nodes&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Enhanced</td>
<td>Breast-conserving surgery</td>
<td>Breast-conserving whole-breast irradiation as part of breast-conserving therapy</td>
</tr>
<tr>
<td>Maximal</td>
<td>Breast reconstruction surgery</td>
<td></td>
</tr>
</tbody>
</table>
ESMO Guidelines - 2009

• Primary systemic therapy is indicated for locally advanced breast cancer (stages IIIA–B) including inflammatory breast cancer [III, B]

• large operable tumors for reducing tumor size in order to possibly perform BCS [I, A]. Before primary systemic therapy a biopsy for histopathology and analyses of predictive factors should be performed.
ESMO Guidelines - 2009

• In addition, for these high-risk patients full clinical staging to rule out metastatic disease is necessary. It may employ chemo- or endocrine therapy based on predictive factors similar to adjuvant treatment.

• Trastuzumab should be considered in the treatment protocol in HER2-positive tumors.

• It should be followed by both surgery and radiotherapy and postoperative systemic adjuvant treatment.
Endocrine therapy - ESMO

• In postmenopausal patients 5 years of tamoxifen alone is still a viable option for certain patient categories. For the use of AIs a switch from tamoxifen to an AI after 2–3 years of tamoxifen or initial use of an AI for 5 years are most commonly accepted strategies [I, A].

• For patients who have completed 5 years of tamoxifen the addition of an AI for a further period of 2–3 years may be recommended in cases with node-positive disease [I, A].
Endocrine therapy - ESMO

• Sequential rather than concurrent administration of cytotoxic and endocrine therapies should be used [II, A].
Treatment modalities according to St Gallen Consensus 2007

<table>
<thead>
<tr>
<th>HER2 status</th>
<th>Highly endocrine responsive</th>
<th>Incompletely endocrine responsive</th>
<th>Endocrine non-responsive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>ET(^a) (consider adding CT according to risk)(^b)</td>
<td>ET(^a) (consider adding CT according to risk)(^b)</td>
<td>CT</td>
</tr>
<tr>
<td>Positive</td>
<td>ET + Trastuzumab + CT</td>
<td>ET + Trastuzumab + CT</td>
<td>Trastuzumab + CT</td>
</tr>
</tbody>
</table>

\(^a\)Endocrine therapy is effective for prevention and ductal carcinoma *in situ* and therefore might be considered even for very low-risk invasive breast cancer.

\(^b\)Within the highly and incompletely endocrine-responsive categories, addition of chemotherapy may be based on degree of steroid hormone receptor expression and level of risk.

ET, endocrine therapy; CT, chemotherapy.
Chemotherapy - ESMO

- The use of anthracyclines for all patients and especially for patients with HER2-positive disease may be recommended. However, for some patients (elderly, cardiac contraindication, etc.) non-anthracycline-containing regimes (CMF) may still be appropriate [I, A]

- Premenopausal women may benefit from 3- to 6-monthly bisphosphonate infusions during the first year to prevent bone loss associated with temporary or permanent hormonal changes during adjuvant chemotherapy [II, B]
Selected adjuvant chemotherapy regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>No. of cycles</th>
<th>Duration of cycle (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMF</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>A–CMF</td>
<td>4–4 (–8)</td>
<td>3–4</td>
</tr>
<tr>
<td>CEF</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>CAF</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>AC–T</td>
<td>4–4</td>
<td>3–3</td>
</tr>
<tr>
<td>AC–T (G-CSF)</td>
<td>4–4</td>
<td>2–2</td>
</tr>
<tr>
<td>DAC</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>FEC–D</td>
<td>3–3</td>
<td>3–3</td>
</tr>
<tr>
<td>FEC100</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>DC</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>

A, doxorubicin; C, cyclophosphamide; D, docetaxel; E, epirubicin; F, fluorouracil; G-CSF, filgrastim; M, methotrexate; T, paclitaxel.
Trastuzumab - ESMO

- HER2 receptor IHC overexpression (3+) or HER2 gene amplification benefit from adjuvant treatment with trastuzumab
- 3-weekly schedule (6 mg/kg) is considered equivalent to a weekly schedule (2 mg/kg)
- Standard duration of adjuvant trastuzumab not yet been established but for the time being 1 year is recommended
- There are no relevant data to support the use of trastuzumab as a standard treatment in women with a primary tumor <1 cm in size and with no axillary node involvement especially in endocrine-responsive disease
Trastuzumab - ESMO

• Trastuzumab may be started in parallel with a taxane, not be given concurrently with an anthracycline. Even when given after an anthracycline-containing regimen, trastuzumab may have cardiotoxic effects and cardiac function should be routinely monitored.

• Avoid trastuzumab in patients with low LVEF <50%

• Administer trastuzumab with endocrine therapy without chemotherapy is not supported by clinical trial evidence.
Follow-up - ESMO

- No data to indicate that performing blood counts, chemistry, chest X-ray, bone scan, liver ultrasound, CT scans of chest and abdomen or any tumor markers such as CA 15-3 or CEA on asymptomatic patients produces a survival benefit [I, A]

- Irrespective of follow-up protocol / frequency of visits, every visit should include history taking, eliciting of symptoms and physical examination. Ipsilateral (after BCS) and contralateral clinical mammography is recommended yearly for premenopausal women and every 1–2 years for postmenopausal women [D]
Follow-up - ESMO

- DEXA scan should be performed for women experiencing a premature menopause (<45 years of age), those on an AI with a baseline T score of less than −1 SD and repeated every 2 years.
Conclusion

• The surgeon’s role in LABC:
  - Biopsy & work-up for systemic disease
  - Post neoadjuvant chemotx. - MRM /BCT
  - For patients with poor physiological reserve & unsuitable for chemotx. – “toilet” mastectomy - controversial
  - Follow-up & management of local recurrence.
References

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