

CHEMOTHERAPY AND BREAST CANCER MANAGEMENT IN NIGERIA

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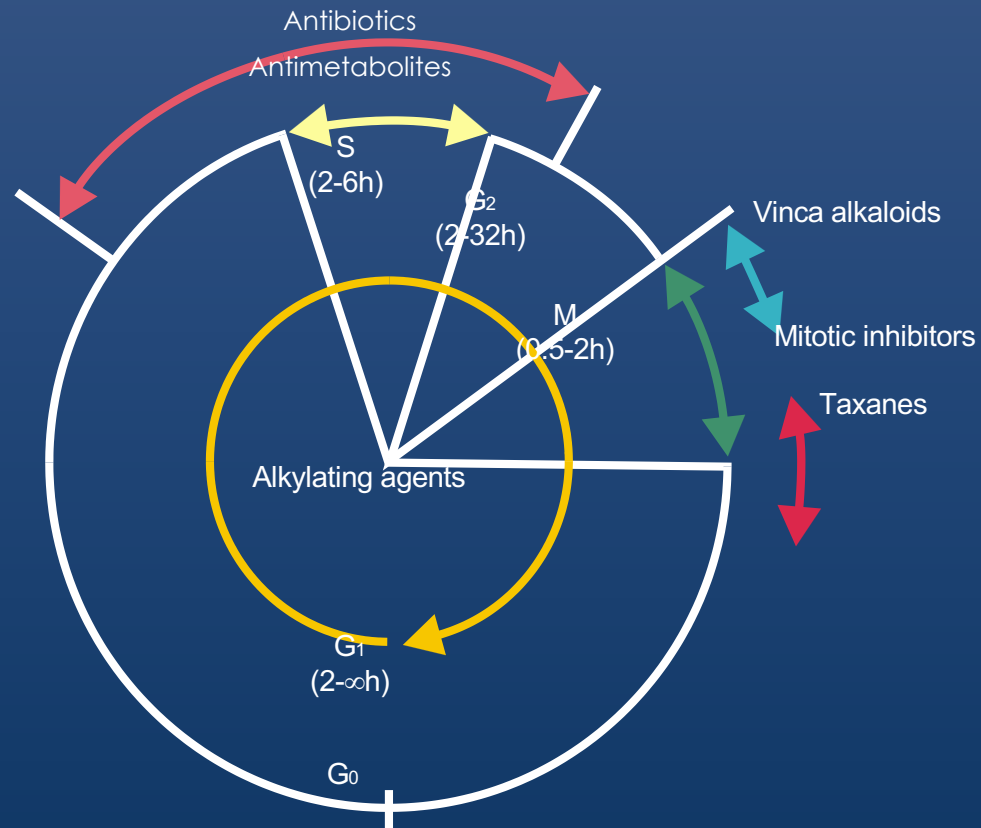
PRINCIPLES OF CHEMOTHERAPY

- Chemotherapeutic/cytotoxic agents are chemical or antimicrobial agents that act on all dividing cells to inhibit their growth or kill them
- Affect tumor cells and normal body cells in a differential manner
 - Affect tumour cells more
 - Affect both equally but normal cells able to recover faster

BREAST CANCER / ACTIVE **CHEMOTHERAPEUTIC AGENTS**

| Type | Agents |
|---|---|
| Alkylating agents | Cyclophosphamide (CPM) Platinum compounds Mitomycin-C (Mit-C) |
| Intercalators | |
| Anthracyclines | Doxorubicin (ADM) Epirubicin |
| Anthraquinones | Mitoxantrone |
| Antimetabolites | Methotrexate (MTX) 5-Fluorouracil (5-FU) |
| Antitubulins | Vinblastine (VLB) Vinorelbine |
| Microtubule superstabilization | Taxols |

SITES OF ACTION OF CYTOTOXIC AGENTS CELL CYCLE LEVEL



WHO AMONG OUR BREAST CANCER PATIENTS SHOULD GET CHEMOTHERAPY?

- Complete removal with Surgery may be achieve but patient may still die of the diz
- Tumor removal may be impossible or Incomplete.
 - Local issues – RTH
 - Local and metastasis - drugs
 - Chemotherapy
 - Hormonal manipulation
 - Immunotherapy/Targeted therapies

CYTOTOXIC CHEMOTHERAPY

- Chemotherapy regimen
 - 1st generation: CMF
 - 2nd generation: Anthracycline backbone
 - 3rd Generation: Taxol backbone
 - 4th generation: Anthracycline-Taxol combo
 - Others: Capecitabine, vinorelbin, carboplatin, gemcitabine
- Chemo integration with Targeted agents
 - Combination of stand alone chemotherapy and targeted agents
 - Antibody-Drug conjugates

TREATMENT DECISIONS IN BREAST CANCER

- Management decision is based on Risk/Benefit ratio.
- Determined by safety and efficacy of choice.
- Treatment is influenced predominantly by patients' and tumour characteristics.
- Treatment is now more individualized -the concept of:
 - personalized care/Customized care or precision medicine

DETERMINANTS OF TREATMENT CHOICES

- Prognostic & Predictive Factors that influence treatment choices
 - Tumour histology
 - Clinical and pathologic characteristics of primary tumour
 - Axillary node status
 - Tumour hormone receptors
 - Tumour HER-2 status
 - Presence of Detectable metastases
 - Patient's comorbidity
 - Age
 - Menopausal status

OTHER CONSIDERATIONS THAT DETERMINE USE OF CHEMOTHERAPY

- Favorable profile: e.g.
 - Excellent performance status, comorbid conditions
 - Financial buoyancy
 - Availability of expertise, facilities and drugs

CRITERIA AND STRATEGY FOR MANAGEMENT DECISION

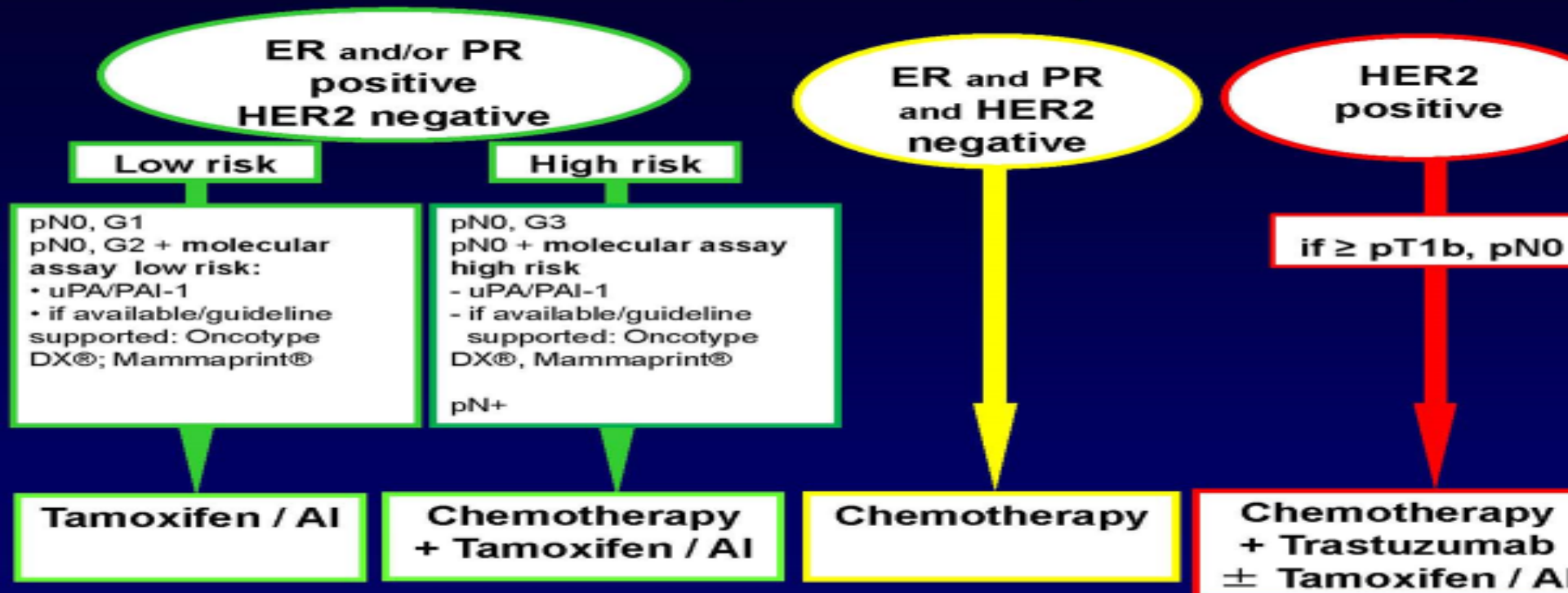
- Diagnosis made
- Disease staged
 - Early breast cancer (Stages I, II)
 - Locally advanced Breast Cancer (Stage III)
 - Metastatic Breast Cancer
- Tumour characterised in terms of Prognostic and Predictive factors
 - IHC: ER/PR status and Her2 neu expression
 - Ki 67 or Mitotic index

EARLY BREAST CANCER: DIAGNOSTIC CRITERIA

- Stage 0: $T_{is}N_0M_0$
- Stage IA: $T_1N_0M_0$
- Stage IB: $T_0N_{1mi}M_0$; $T_1N_{1mi}M_0$
- Stage IIA: $T_0N_1M_0$; $T_1N_1M_0$; $T_2N_0M_0$

CHEMOTHERAPY IN EARLY BREAST CANCER

Treatment Concepts in *Early BC*: Today

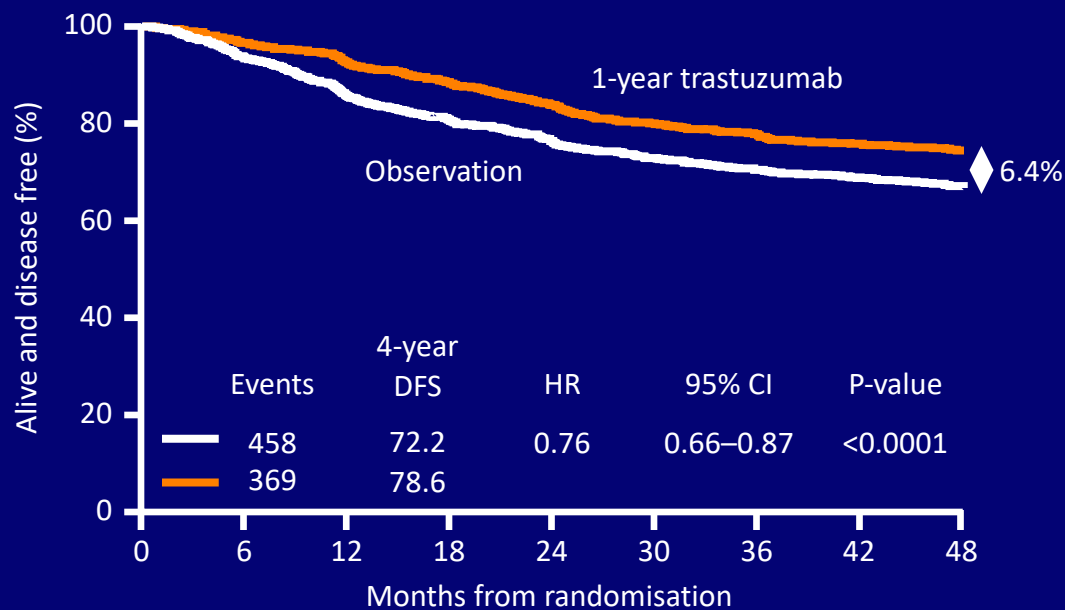


Harbeck, N. et al. *Cancer Treat Rev.* 2010; May 27[epub ahead of print].

CHEMOTHERAPY IN EARLY BREAST CANCER IN NIGERIA

- Mostly used as an adjuvant treatment or sometimes as neoadjuvant
- Best of centers in Nigeria use 4th generation regimen as 1st line chemotherapy
 - Combination of Anthracycline based regimen X 4 doses and then taxol based regimen x 4 doses (or weekly paclitaxel x 12 doses)
 - Dose-dense schedules with prophylactic G-CSF are acceptable, particularly in patients with highly proliferative tumours.
 - Other regimen in common use: TC, TAC, CA, CAF, CMF

DFS benefits of 1-year adjuvant trastuzumab persist at 4-year follow-up (ITT) – HERA study



| | | | | | | | | | |
|---------|------|------|------|------|------|------|------|------|-----|
| No. | 1698 | 1564 | 1440 | 1363 | 1297 | 1240 | 1180 | 992 | 712 |
| at risk | 1703 | 1619 | 1552 | 1485 | 1414 | 1352 | 1280 | 1020 | 854 |

CI, confidence interval; HR, hazard ratio; ITT, intent to treat

Gianni, et al. 2011

Trastuzumab

- 1 year of adjuvant trastuzumab, used either concurrently with chemotherapy or sequentially, is a standard of care adjuvant treatment of HER2+ve early breast cancer.
- Trastuzumab given concurrent with chemotherapy is better than sequential use.
- Trastuzumab administered for <1 year is suboptimal but better than no trastuzumab.
- Current evidence does not support continuation of adjuvant trastuzumab beyond 1 year.
- Double Her 2 blockade with Trastuzumab and Pertuzumab has changed the standard of care



CHEMOTHERAPY IN LOCALLY ADVANCED BREAST CANCER

- LABC include
 - LABC that may be operable at presentation
 - Stage IIIA: T3 with any N; N2 with any T1–T3
 - LABC that is inoperable at presentation
 - Stage IIIB: T4a, chest wall; T4b, skin; T4c (a&b)
 - Stage IIIC: N3 with any T
 - T4d (inflammatory breast cancer)

CHEMOTHERAPY IN LOCALLY ADVANCED BREAST CANCER

- Neoadjuvant chemotherapy has been accepted as the standard of care in women with locally advanced breast cancer
 - NSABP B-18: Neoadjuvant CA x4 equivalent to adjuvant CA x4
 - NSABP B-27: Neoadjuvant CA + Docetaxel improved BCT rate and pCR rate (26% vs 13%) than adjuvant regimen

CHEMOTHERAPY IN LABC: TREATMENT INTENT

- Neoadjuvant systemic treatment, mostly with chemotherapy
 - Improve surgical options (BCT, mastectomy, cosmesis)
 - Obtain response information
 - Early response predicts pCR
 - pCR predicts long term disease free survival
 - Tailor subsequent treatment
 - Partial response make case for adjuvant chemotherapy with another drug or maintenance treatment with capecitabin
 - Non response make case for early introduction of local treatment

NEOADJUVANT CHEMOTHERAPY IN LABC

- Best of centers will normally complete fully chemotherapy as neoadjuvant before local treatment of the breast cancer
 - To allow opportunity for pCR
- Anthracycline based regimen is standard of care in all LABC
 - the threshold for anthracycline-associated cardiac toxicity should not be exceeded – prefer 4th Generation regimen
- Taxanes should be added but sequenced with Anthracyclines
 - Weekly paclitaxel better than 3 wkly
 - 3wkly docetaxel standard but must have filgrastim
- Platinum compound improved pCR in Triple negative tumours

TREATMENT OF MBC

- Palliation to improve symptoms in advanced lesions e.g. pain, dyspnea
- Prolongation of survival (Oligometastatic breast cancer)
- Treatment options
 - Chemotherapy
 - Hormonal treatment
 - Targeted therapies

SYSTEMIC TREATMENT CHOICES IN MBC

- The choice of therapy based on several factors:
 - Previous therapies and response to them
 - Disease-free interval
 - Endocrine responsiveness
 - HER2 status
 - Tumour burden (defined as number and site of metastases)
 - Menopausal status
 - Biological age and co-morbidities (including organ dysfunction)
 - Performance status
 - Need for rapid disease/symptom control
 - Socio-economic and psychological factors
 - Patient's preference
 - Available therapies in the local environment

CHEMOTHERAPY IN MBC

- Who should get chemo
 - Patients that need aggressive therapy
 - Very aggressive tumours
 - Visceral involvement
 - Young patients
 - Triple negative tumours
 - Endocrine resistance
 - Best palliation achieved with chemo

CHEMOTHERAPY AGENTS/REGIMENS FOR MBC

ANTHRACYCLINE-CONTAINING

Doxorubicin or epirubicin monotherapy or with cyclophosphamide

Fluorouracil/doxorubicin/cyclophosphamide or
fluorouracil/epirubicin/cyclophosphamide

TAXANE-CONTAINING

Paclitaxel monotherapy (weekly or 3-weekly)

Docetaxel monotherapy (3-weekly or weekly)

Anthracycline (doxorubicin or epirubicin)/ taxane (paclitaxel or docetaxel)

Docetaxel/capecitabine, Paclitaxel/gemcitabine, Paclitaxel/vinorelbine,
Paclitaxel/carboplatin

NON-ANTHRACYCLINE-CONTAINING

Cyclophosphamide/methotrexate/fluorouracil

Platinum-based combinations (cisplatin+fluorouracil;
carboplatin+gemcitabine)

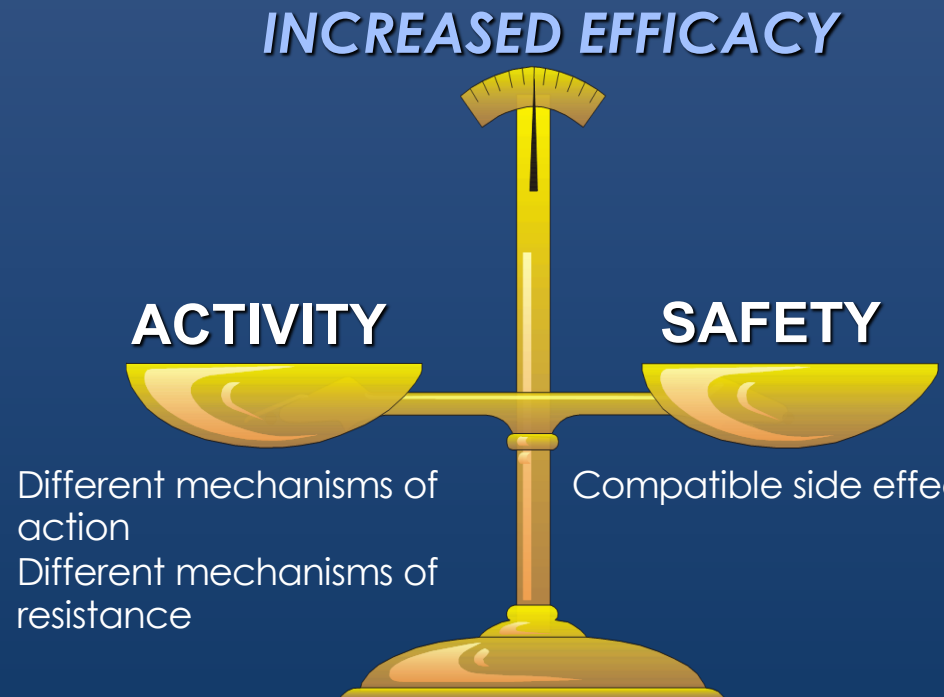
Capecitabine, vinorelbine, capecitabine+vinorelbine, vinorelbine+/-
gemcitabine

PRINCIPLES OF CHEMOTHERAPY IN MBC

- Concept of treatment continuum in responders (1st, 2nd, 3rd line therapies) based on concept of non-overlapping toxicities
- Duration of each regimen and number of regimens should be tailored to each individual patient.
- Single agent (monotherapy) VS combo
- Maintenance therapy for long duration
 - Capecitabine even at low doses has therapeutic effect
- Mind ceiling doses and limiting side effects

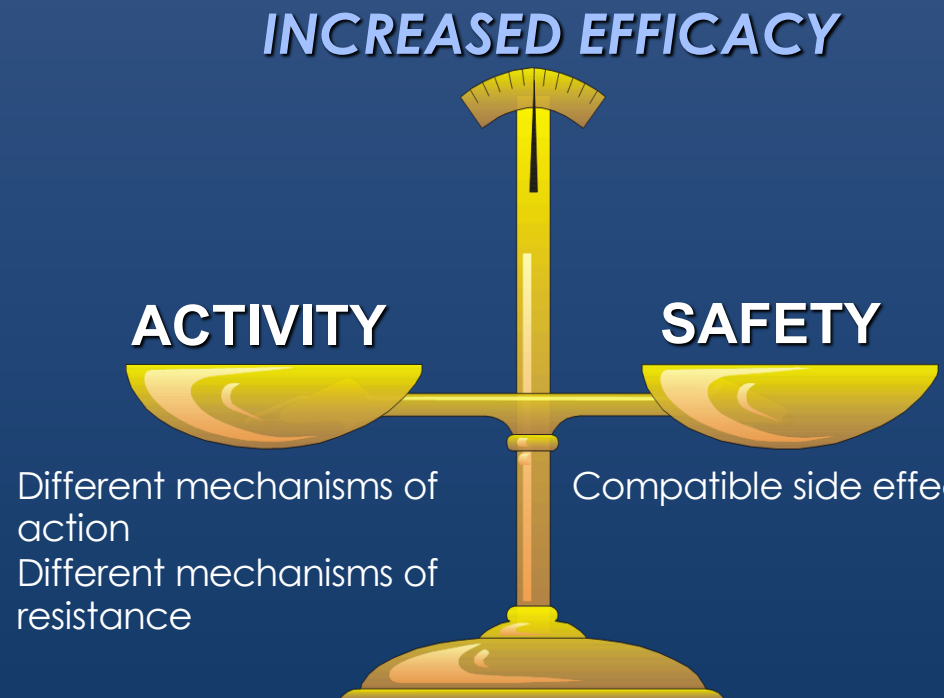
CARE OF PATIENTS ON CHEMOTHERAPY

- Must balance toxicity with expected benefits
- Toxicity best handled when experts in the field give the drug
- Acute toxicity in rapidly dividing cells

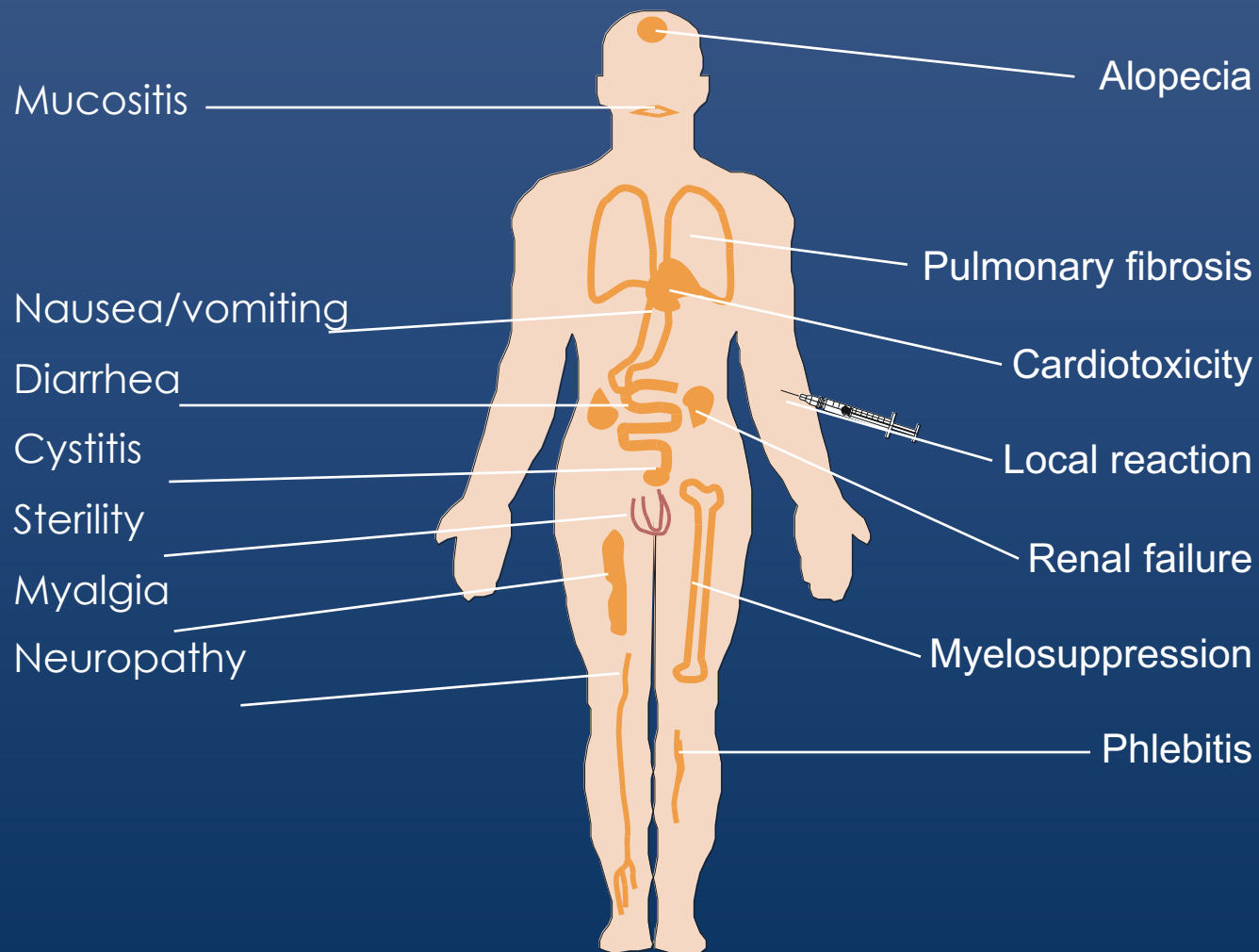


CARE OF PATIENTS ON CHEMOTHERAPY

- Prechemotherapy workup:
 - FBC
 - SEUC
 - LFT
 - 2D Echo

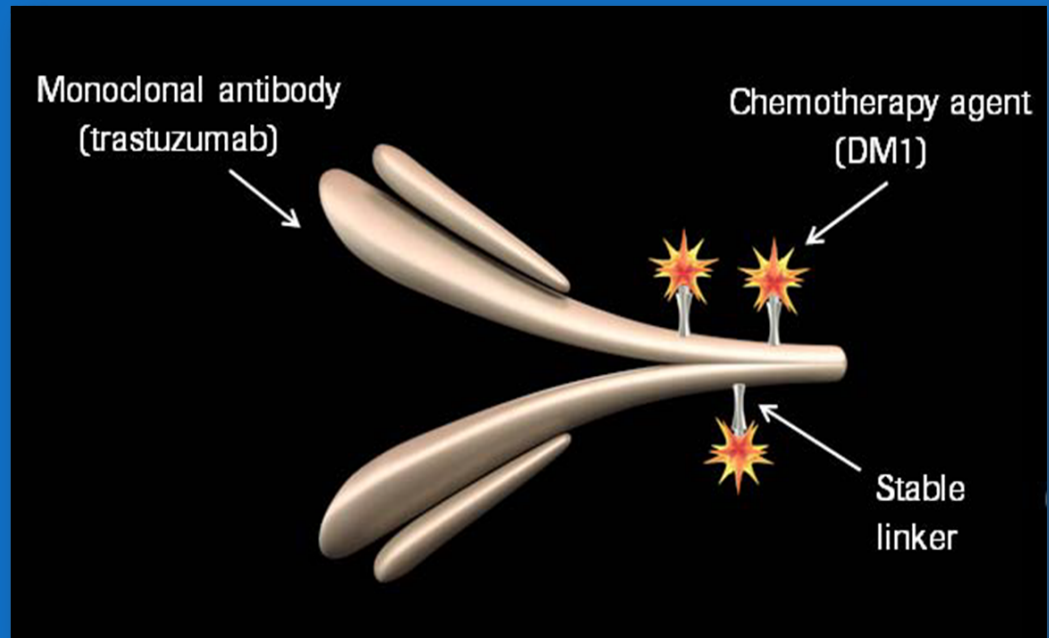


SIDE EFFECTS OF CHEMOTHERAPY



NEW AREAS IN CHEMOTHERAPY FOR BREAST CANCER

- TNBC:
 - Ixabepilone: a microtubule stabilizer, useful in taxane resistance cases.
 - Eribulin: a tubule stabilizer still in clinical trial for resistant dz.
- Hers +ve BC:
 - Targeted chemotherapy Antibody-Drug Conjugates (ADC).
Trastuzumab
emtansine (T-DM1)



CONCLUSION

- Chemotherapy is a key component of the treatment armamentarium for every stage of breast cancer
- The toxicity profiles demands utmost care by Oncologists in the choice of agents or combinations in order to get the best response with the minimum side effects
- Proper use of the agents will afford our patients opportunities for curative treatment or the best palliation possible for their condition.



THANK YOU