THE LANDSCAPE OF SYSTEMIC CANCER THERAPY IN AFRICA

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Disclaimer

- I have no conflicts of interest to declare.
- I have not practiced in other African countries, my presentation is based predominately on the South African experience and on contact I have had with African colleagues at loco-regional meetings and advisory board meetings.
OVERVIEW

- Incidence of Cancer
- Resource Considerations and Challenges
- Systemic Breast Cancer treatments
- Systemic Colon Cancer Treatments
- Conclusions
INCIDENCE OF CANCER

- In areas across the continent where infectious diseases, infant mortality, maternal mortality, civil war and violence have a major impact on life expectancy - cancer incidence associated with an aging population is not the greatest health care focus or concern.

- South African data is quite similar to international age specific data on the incidence of cancer that is biased towards a much higher incidence in later years.

- In South Africa, and elsewhere in Africa, the incidence of cancer has been steadily increasing as the populations urbanize and adopt different lifestyles and diets.
INCIDENCE OF CANCER

- South Africa is faced with the grave reality that life expectancies across racial groups still differ dramatically and therefore, if we are to factor in age related cancer, so too is the likely cancer incidence among specific groups.

- The black community in South Africa has by far the shortest life expectancy at birth. In addition, the age structure differs substantially among the race groups.
POTENTIAL EFFECTS OF BETTER ACCESS TO CARE

- Improvements in general medical outcomes, resulting in increased life expectancy implies an ageing population.
- This would result in increasing incidence of cancer and the need for cancer care and resources.
- So paradoxically.. We can (hopefully) expect a dramatic increase in cancer incidence with age in South Africa and Africa as a whole as health care to the wider population improves and we work towards less disparity in health care.
- An article in The Lancet indicated experience elsewhere in the world where perceived cancer incidence increased dramatically, from similar levels to South Africa’s, following the introduction of proper diagnostic facilities such as a screening program.
INCIDENCE AND SCREENING

- True screening is not available through most of Africa within the public health structures tasked with the care of the vast majority of Africa’s population.
- Even within South Africa there is a huge disparity across the various regions, in urban areas the density and penetration of screening programs is starting to make inroads, however in peripheral and rural areas this is not the case.
- The dire scenario of only 3 mammogram units for a neighbouring country can in no way begin to offer screening to a population, rather an attempt to facilitate the diagnosis of already advanced disease.
- Poorer outcomes are unfortunately the consequence.
- It is only within the affluent and insured minority of patients in Africa that anything approaching a screening program is seen.
- There is currently a big push by the South African department of Health to formulate a white paper with protocols for screening and up referral for breast and cervical cancer that is a vast step in the right direction to improve health care.
INCIDENCE OF CANCER

- The Medical Research Council (MRC) gives a total cancer incidence of cancer as:
  148.9/100,000 in males and
  134.9/100,000 in females,
- BUT it finds dramatically different incidence rates between the race groups.
  - White South Africans have cancer incidence of
    277 and 230/100,000 for males and females,
  - Black South Africans have cancer incidence of
    only 97.1 and 103.7/100,000 for males and females
INCIDENCE OF CANCER

- HOWEVER International experience has shown that when similar levels of care are available there is not such a significant difference in incidence between race groups.
Breast Cancer Incidence

- In South Africa and in developed countries, breast cancer is the most common cancer of women having overtaken cervical cancer.
- Worldwide, breast cancer is the cause of more than 500,000 deaths annually.
- Based on incidence in 2007 the calculated lifetime risk of Breast Cancer in females in South Africa is 1:35
- In developed countries, the lifetime risk of breast cancer is approximately 1:10
- While the reduction (both relative and real) in cervical cancer incidence can in part be ascribed to some penetrance of screening programs at local clinics. As yet the impact of HPV vaccination is not a contributing factor.
In South Africa < 16% of the population is covered by medical insurance

- Of which < 50% of these have access to upper end funding models which would include cover monoclonal antibodies, tyrosine kinase inhibitors and immunotherapy
- The public sector is required to care for around 84% of population

Our public sector under the current model would not be ideal to manage an increasing incidence of cancer BUT effective planning and retention of expertise can increase the capacity.
WHY MEDICAL BILLS ARE KILLING US
BY STEVEN DRILL
From 1990 to 2008, overall costs of treating cancer more than tripled in nominal dollars and more than doubled in inflation-adjusted dollars.

Cancer treatment in the US cost more than $90 billion in 2006.
- Just under 5% of total US spending on medical care.
CHALLENGES:

- Identify drivers of cost
- Identify how we can reduce costs?
- Identify how we can maintain or improve quality?
- And still meet demand?
CHALLENGE: UNDERSTANDING WHAT DRIVES THE COST OF CANCER CARE

- Demographics
- Behaviour
  - Tobacco, obesity, adherence to screening
- Novel Interventions
  - Drugs,
  - Genetic Tests,
  - Radiation Therapy,
  - Imaging
- Over-Utilization
  - Lack of Evidence based practice,
  - Incentive structure,
  - Defensive medicine,
  - Lack of communication/care delivery inconsistent with patients preferences
Overall increase in spending for cancer care reflects increases in both price and quantity of care
- Between 1991 and 2002, the proportion of breast cancer patients receiving chemotherapy and the average cost of the chemotherapy both roughly doubled. Similar trends have been observed for other types of cancer.

The increases in price and quantity reflect the introduction of new medical technology
- Newer cancer therapies are more expensive than the prior standard of care;
- Newer drugs expand the pool of treatment candidates (e.g. because of broader indications, reduced side effects).
- Drug spending has been growing faster than costs for physicians’ services or hospital care
What drives increased spending on pharmaceuticals?

- Number of prescriptions dispensed (42%)
  - Average prescriptions per capita increased from 7.9 to 12.4 between 1994 and 2006

- Types of prescriptions (34%)
  - newer, higher-priced drugs replacing older, less-expensive drugs

- Manufacturer price increases for existing drugs (25%)

RISING CANCER CARE COSTS

Most Expensive Cancers in U.S. in 2010

- Breast $16.5 billion
- Colorectal $14.1 billion
- Lymphoma $12.1 billion
- Lung $12.1 billion
- Prostate $11.9 billion

600% Increase in spending over 30 years....
BREAST CANCER SYSTEMIC TREATMENT
ADJUVANT CHEMOTHERAPY

- EBCTCG meta-analysis of 47 trials comparing combination chemotherapy to no chemotherapy showed a significant reduction in mortality in patients receiving chemotherapy regardless of nodal status, ER status or whether tamoxifen was given.

- Benefit of chemotherapy varied with age
  - < 50yrs 10yr survival improved from 71 to 78% in node negative pts and 42 to 53% node positive
  - 50-69 yrs 10yr survival improved from 67 to 69% in node negative pts and 46 to 49% in node positive pts
# Risk Stratification to Define Rx

<table>
<thead>
<tr>
<th></th>
<th>Low risk (has all listed factors)</th>
<th>Intermediate risk (risk classified between the other 2 categories)</th>
<th>High risk (has at least 1 listed factor)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor size</td>
<td>$\leq$1cm</td>
<td>1-2cm</td>
<td>$&gt;2$cm</td>
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<tr>
<td>ER or PR Status</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
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<td>Tumor grade</td>
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<td>Grade 2-3</td>
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<td>Negative</td>
<td>Positive</td>
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<td>Low fraction</td>
<td>Intermediate fraction</td>
<td>High fraction</td>
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<tr>
<td>Nodes positive</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
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</table>


ADJUVANT SYSTEMIC TREATMENT RISK MODELS

○ Magee Score
  • In a study from University of Pittsburgh standard histopathologic factors and immunohistochemical markers can be used to estimate the recurrence score validated on a separate set of over 200 cases, sent for clinical oncotyping DX®. Multiple linear regression analysis was performed to model the prediction of the oncotyping DX® RS by Nottingham Score, Ki-67 labelling index (0-100), tumor size (in cm.), H-scores (range: 0-300) for ER and PR, and HER2 status (negative, equivocal or positive).

○ Adjuvant Online
  • Adjuvant! Online is a web-based application designed to provide 10 years survival probability of patients with breast cancer. However, this model is currently unavailable as it is being upgraded.

○ Predict Tool
  • An online prognostication and treatment benefit tool. The survival estimates are presented both with and without adjuvant therapy (hormone therapy, chemotherapy and trastuzumab), and provided for 5 and 10 years following surgery. Development of the model was a collaborative project between the Cambridge Breast Unit, University of Cambridge Department of Oncology and the Eastern Cancer Information and Registration Centre (ECRIC) and was supported by an unrestricted educational grant from Pfizer Limited.
ADJUVANT SYSTEMIC TREATMENT RISK MODELS

- **Mammaprint®**
  - 70-gene signature test that among women with early-stage breast cancer who were at high clinical risk and low genomic risk for recurrence, the receipt of no chemotherapy on the basis of the 70-gene signature led to a 5-year rate of survival without distant metastasis that was 1.5 percentage points lower than the rate with chemotherapy.

- **Oncotype®**
  - Oncotype DX looks at the expression of a panel of 21 genes within a tumour to determine a Recurrence Score. The Recurrence Score is a number between 0 and 100 that corresponds to a specific likelihood of breast cancer recurrence within 10 years of the initial diagnosis.
**B-20 Results: Tam vs Tam + Chemo**

**Low RS**
- Low Risk Patients (RS < 18)
- \( p = 0.61 \)
- TAM + Chemo: 218 events, 8
- TAM: 135 events, 4

**Int RS**
- Int Risk Patients (RS 18-30)
- \( p = 0.39 \)
- TAM + Chemo: 89 events, 9
- TAM: 45 events, 4

**High RS**
- High Risk Patients (RS ≥ 31)
- \( p < 0.001 \)
- TAM + Chemo: 117 events, 13
- TAM: 47 events, 18

- 28% absolute benefit from tam + chemo

ADJUVANT CHEMOTHERAPY

- **First-generation regimens**
  - First-generation regimens are considered less effective than second- or third-generation regimens, however CMF is a reasonable alternative for patients who have contraindications to anthracycline and taxane therapy.
  - CMF
  - AC for four cycles

- **Second-generation regimens**
  - Second-generation regimens are more effective than first-generation protocols.
  - FAC for six cycles
  - FEC for six cycles
  - Dose-dense AC-Paclitaxel with colony-stimulating factor (CSF) support
  - TC for four cycles shown to be more effective than AC

- **Third-generation regimens**
  - Third-generation regimens are more effective than some second-generation regimens and include anthracyclines and taxanes.
  - 4AC-Paclitaxel weekly for 12 wk
  - TAC six cycles with granulocyte CSF support
  - 3FEC-3Docetaxel
  - 4FEC-Paclitaxel weekly for eight cycles
ADJUVANT TRASTUZUMAB

- Trastuzumab is a humanized monoclonal antibody targeting tumor cells overexpressing Her2/neu
- 15-20% of pts with breast cancer overexpress Her2/neu marking for poorer prognosis more aggressive disease.
- 4 studies have addressed the merit of Trastuzumab in the adjuvant setting. All published in NEJM
- These 4 trials enrolled over 11 000 pts
  - HERA
  - Combined B31 & N9831 analysis
  - BCIRG006
Trastuzumab for 1 year improves OS for women with HER2-positive EBC.

- HERA H 1 year: Not confounded by crossover (2 years)
- HERA H 1 year: Confounded by crossover (4 years)
- NSABP B-31 / N9831 AC→PH (3 years)
- BCIRG 006 AC→DH (5 years)
- BCIRG 006 DCarboH (5 years)

Median follow-up, years

Hazard ratio

Favours Herceptin

Favours no Herceptin

OS, overall survival; Carbo, carboplatin

References:
Perez et al 2007; Smith et al 2007; Gianni et al 2009; Slamon et al 2009
ADJUVANT TRASTUZUMAB

- Adjuvant Chemotherapy protocols with Trastuzumab
  - 4AC-Paclitaxel weekly for 12 weeks or 3 weekly for four cycles given concurrently with trastuzumab for a 1-y total duration of trastuzumab therapy.
  - 4AC-4Docetaxel plus trastuzumab 1 y of trastuzumab.
  - 6TC with trastuzumab to complete 1-y total duration of trastuzumab therapy
- Of Note: The PHARE comparing 6 months to 12 months of adjuvant Herceptin was unable to show non-inferiority of the 6month protocol
Neoadjuvant Systemic Treatment
Neoadjuvant Chemotherapy Protocols

- 4AC-Paclitaxel weekly for 12 wk
- TAC six cycles with granulocyte CSF support
- 3FEC-3Docetaxel
- 4FEC-Paclitaxel weekly for eight cycles
- Dose-dense AC-Paclitaxel with colony-stimulating factor (CSF) support
- TC for four cycles
NEOADJUVANT CHEMOTHERAPY PROTOCOLS WITH TRASTUZUMAB

- 4AC-Paclitaxel weekly or 3 weekly for four cycles given concurrently with trastuzumab for a 1-y total duration of trastuzumab therapy.
- 4AC-4Docetaxel plus trastuzumab 1 y of trastuzumab.
- 6TC with trastuzumab to complete 1-y total duration of trastuzumab therapy
- ? Plus Pertuzumab or Lapatinib
- Remember to always consider clinical trials.
Patients with hormone receptor-positive advanced breast cancer are appropriate candidates for endocrine therapy if they have no or little symptoms related to their disease.

Patients who present with any of the following disease characteristics are optimal candidates for endocrine therapy:

- No or limited visceral metastases
- Bone-only metastatic disease
- Slowly progressive disease
FIRST LINE TREATMENT ABC

- Depends if this is the initial presentation.
- If not the initial presentation depends on what treatment the patient had in the adjuvant setting.
- Depends if the patient is premenopausal or postmenopausal.
HORMONE RECEPTOR POSITIVE
HER 2 NEGATIVE
ADJUVANT HORMONE TREATMENT

Options include:

- Ovarian suppression or ablation for premenopausal women
- Selective estrogen receptor modulator (SERM)
- Combination treatment (tamoxifen/AIs ± ovarian suppression)
- A choice between them is based on patient and physicians preferences.
- All the above options are available in the public and private sector
For patients with disease progression following first-line endocrine therapy, second-line hormonal treatment is a reasonable option, provided they are not symptomatic and their disease continues to be slowly progressive.

Patients who develop symptoms due to disease progression and those with rapidly progressive metastatic disease should be treated with chemotherapy.
3rd Line Premenopausal

- Clinical trial needs to be considered,
- All lines of chemotherapy can be considered once hormonal therapies have been exhausted.
POSTMENOPAUSAL

Fulvestrant is an estrogen receptor antagonist used in the treatment of postmenopausal women. Fulvestrant blocks ER dimerization and DNA binding, increases ER turnover, and inhibits nuclear uptake of the receptor.

One trial suggests that fulvestrant has equivalent efficacy to anastrozole. In the FIRST (First-Line Study Comparing Endocrine Treatments) trial, when compared with anastrozole, fulvestrant resulted in:

- A similar ORR (36 percent in both arms)
- A longer time to progression (median, 23 versus 13 months, HR 0.66; 95% CI 0.47-0.92)

Overall survival was not reported for this trial.

At this time, fulvestrant is probably not the first option in the first-line setting in SA if one is to consider cost and that it is not available in the state sector.
There is a lack of clinical trials to address the optimal sequence of therapy from the first to the second-line setting.

The available options include:
- tamoxifen,
- a non-cross-resistant AI,
- fulvestrant,
- endocrine therapy plus the mammalian target of rapamycin (mTOR) inhibitor, everolimus, in the second-line setting.
- A choice between them should be individualized based on prior treatment received and a patient's co-morbidities.
2ND LINE POSTMENOPAUSAL

- The benefit of everolimus plus the steroidal AI, exemestane versus exemestane alone, was shown in the Breast Cancer Trials of Oral Everolimus (BOLERO-2) trial
- The combination of exemestane and everolimus resulted in:
  - An improvement in PFS (median, 7 versus 3 months; HR for mortality 0.43, 95% CI 0.35-0.54)
  - Higher ORR (9.5 versus 0.4 percent)
BOLERO-2: PRIMARY ENDPOINT, PFS (18-MONTH FOLLOW-UP, LOCAL ASSESSMENT)

HR=0.45 (95% CI: 0.38-0.54)
Log-rank P value: < .0001

Kaplan-Meier medians
EVE 10 mg + EXE: 7.8 months
PBO + EXE: 3.2 months

Censoring times
EVE 10 mg + EXE (n/N=310/485)
PBO + EXE (n/N=200/239)

HR=0.45 (95% CI: 0.38-0.54)
Log-rank P value: < .0001

Kaplan-Meier medians
EVE 10 mg + EXE: 7.8 months
PBO + EXE: 3.2 months

Number of patients still at risk

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CI, confidence interval; EVE, everolimus; EXE, exemestane; HR, hazard ratio; PBO, placebo; PFS, progression-free survival.
BOLERO-2: ORR AND CBR
(18-MONTH FOLLOW-UP, LOCAL ASSESSMENT)

CBR, clinical benefit rate; EVE, everolimus; EXE, exemestane; PBO, placebo; ORR, overall response rate.
Overall Survival (October 2010)

Hazard ratio = 0.32; 95% CI 0.15-0.68
Exploratory log-rank: $P = .0019$

Patients at risk

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<th>Time, mo</th>
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Phase II Study of Letrozole ± Palbociclib (PD-0332991) in ER+, HER2- MBC

Part 1
Stratified by disease site (visceral, bone only, or other); disease-free interval (> 12 vs ≤ 12 mos from end of adjuvant to recurrence or de novo advanced disease)

Postmenopausal women with ER-positive, HER2-negative advanced breast cancer (N = 66)

- Palbociclib 125 mg QD + Letrozole 2.5 mg QD
- Letrozole 2.5 mg QD

Part 2
Stratified by disease site (visceral, bone only, or other); disease-free interval (> 12 vs ≤ 12 mos from end of adjuvant to recurrence or de novo advanced disease)

Postmenopausal women with ER-positive, HER2-negative advanced breast cancer, CCND1 amp, and/or p16 loss (N = 99)

- Palbociclib 125 mg QD + Letrozole 2.5 mg QD
- Letrozole 2.5 mg QD

All patients continued assigned treatment until disease progression, withdrawal of consent, or unacceptable toxicity with follow-up tumor assessment every 2 mos.

**Letrozole ± Palbociclib in ER+, HER2- MBC: PFS**

**Patients at Risk, n**
- **Palb + LET** (n = 84):
  - 84 75 60 53 43 35 25 18 15 14 9 5 3 1
- **LET** (n = 81):
  - 81 57 33 29 22 17 11 6 5 4 3 3 1 1

**Events, n (%)**
- Palb + LET: 21 (25)
- LET: 40 (49)

**Median PFS, mos (95% CI)**
- Palb + LET: 26.1 (12.7-26.1)
- LET: 7.5 (5.6-12.6)

**HR (95% CI)**
- 0.37 (0.21-0.63)

**P value**
- < .001

HER 2 POSITIVE PATIENTS
1st Line Treatment
H0648g pivotal trial confirmed predictive value of HER2

IHC 2+ tumours were not confirmed for HER2 positivity by in situ hybridisation
Subgroup analysis, p value not reported

IHC 3+ taxane subgroup
- Herceptin + paclitaxel (n=68)
- Paclitaxel (n=77)

Probability of survival (%)

Time (months)

0 5 10 15 20 25 30 35 40 45

6.9 months

+40%

17.9 24.8

Smith 2001
Trastuzumab has changed the natural history of HER2-positive disease

- Patients with HER2-positive MBC now have comparable outcomes with HER2-negative MBC

Dawood et al 2010
GBG-26: continuation of Trastuzumab beyond progression provides benefit BUT probably not “value”

Probability of progression (%)

Time (months)

Hazard ratio = 0.69
p = 0.034

Median TTP in months (time between randomisation and documented disease progression or disease-related death)

Median follow-up: 15.6 months

Not within EMEA-approved indication for Herceptin

von Minckwitz et al 2009
TRIPLE NEGATIVE BREAST CANCER
1\textsuperscript{st} Line Treatment

- Consider a clinical trial if available.
- Possible Trials with checkpoint inhibitors if PDL\textsubscript{1} positive
- Consider testing for Androgen Receptor
Hormonal Anti-androgen Treatment

- Endocrine therapy is ineffective in breast cancer patients with classic hormone receptor-negative disease.

- However, in ER- and PR-negative disease there is a subset with the AR expression that is predictive to respond to antiandrogen therapies.

- Unfortunately, the role of anti-AR targeted drugs is limited. TNBC represents 20 % of the disease, and 10 % of that is AR positive, so only 2 % of overall breast cancer cases may benefit from this form of treatment.

- A phase II study explored bicalutamide in the subset of AR-positive metastatic disease. In this study, AR was tested by IHC and considered positive if the nuclear staining was greater than 10 %.

- Patients were treated with bicalutamide at a dose of 150 mg daily. The primary endpoint of this study was defined as the total number of patients who showed a CR, PR, or stable disease (SD) after 6 months.

- The percentage of patients showing clinical benefit (CR, PR, and SD) was 19 % (95 % CI 7–39 %) for bicalutamide.

- The median PFS was 12 weeks (95 % CI 11–22 weeks).

- Bicalutamide was well tolerated with moderate activity in patients with ER- and PR-negative, AR-positive breast cancer.
COLORECTAL CANCER SYSTEMIC TREATMENT
### Table. Estimated Drug Costs for Eight Weeks of Treatment for Metastatic Colorectal Cancer.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Drugs and Schedule of Administration</th>
<th>Drug Costs* $</th>
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<tbody>
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<td><strong>Regimens containing fluorouracil</strong></td>
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<tr>
<td>Mayo Clinic</td>
<td>Monthly bolus of fluorouracil plus leucovorin</td>
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<td>Roswell Park</td>
<td>Weekly bolus of fluorouracil plus leucovorin</td>
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<td>LV5FU2</td>
<td>Biweekly fluorouracil plus leucovorin in a 48-hr infusion</td>
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<td>LV5FU2 with biweekly irinotecan</td>
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<td>LV5FU2 with biweekly oxaliplatin</td>
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<td><strong>Regimens containing bevacizumab or cetuximab</strong></td>
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</tr>
<tr>
<td>Irinotecan with cetuximab</td>
<td>Weekly irinotecan plus cetuximab</td>
<td>30,790</td>
<td></td>
</tr>
<tr>
<td>FOLFIRI with cetuximab</td>
<td>FOLFIRI and weekly cetuximab</td>
<td>30,675</td>
<td></td>
</tr>
</tbody>
</table>

*Costs represent 95 percent of the average wholesale price in May 2004.*
RISING COST

- Ziv-Aflibercept Met CRC Median OS 1m > placebo (13 vs. 12 months)
- Regorafenib Met CRC Median OS 1.4m > placebo (6.4 vs. 5 months)
ADDRESSING SOME DRIVERS OF COST OTHER THAN DIRECT DRUG COSTS: ASCO’s TOP 5

- For patients with advanced solid-tumour cancers who have a poor performance status and are unlikely to benefit, do not provide unnecessary anticancer therapy, such as chemotherapy, but instead focus on symptom relief and palliative care.

- Do not use PET, CT and radionuclide bone scans in the staging of early prostate cancer at low risk for metastasis.

- Do not use PET, CT and radionuclide bone scans in the staging of early breast cancer at low risk for metastasis.

- For individuals who have completed curative breast cancer treatment and have no physical symptoms of cancer recurrence, routine blood tests for biomarkers and advanced imaging tests should not be used to screen for cancer recurrences.

- Avoid administering colony stimulating factors (CSFs) to patients undergoing chemotherapy who have less than a 20 percent risk for febrile neutropenia.
REALITY CHECK FOR SYSTEMIC TREATMENT

- Except for the Haematological Malignancies and GIST Tyrosine kinase inhibitors are not available to the majority of patients.
- Except for the Haematological Malignancies Monoclonal antibodies are not available to the majority of patients.
- Outside of clinical studies none of our patients in the public sector are likely to access newer cancer therapies.
Existing Strategies to Limit Costs of Oncology Drugs

- More choices within therapeutic class
- Tiered formularies
- Step edits
- Prior authorization
- Quantity limits
- Cost transparency

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**Strengths Current Models:**

- Structures that are essentially not for profit.
- Academically minded treatment guidelines and clear treatment exit criteria.
- Multidisciplinary review included in guideline criteria.
- Quality peer review and appeals process.
- Broader access to quality cancer care through like minded role players coming together to increase patient access to QUALITY care, used RATIONALLY and in the most APPROPRIATE setting.
- Systems with outcomes driven to benefit patients and funders.
CONCLUSION

- The dichotomy of healthcare access across our continent is pronounced, it is the comfort of the adequately insured and discomfort of those who are not.
- The inequality of the haves versus the have-nots.
- The will of some of those in positions of power as opposed to the apathy of others.
CONCLUSION

“It was the best of times, it was the worst of times, it was the age of wisdom, it was the age of foolishness, it was the epoch of belief, it was the epoch of incredulity, it was the season of light, it was the season of darkness, it was the spring of hope, it was the winter of despair.”
— Charles Dickens, A Tale of Two Cities
THANK YOU