Update on Palliative Oncology
Palliative Chemotherapy

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Outlines

• Update incidence of cancer patients in Thai and worldwide (US)
• Palliative Chemotherapy
• Palliative Care Framework

• Update in palliative chemotherapy in several cancers
*** Focus in the common cancer patients
– Lung cancer
– Colon cancer
– Breast cancer

Estimated New Cases

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<thead>
<tr>
<th>Cancer Type</th>
<th>Male</th>
<th>Female</th>
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<tr>
<td>Lung &amp; bronchus</td>
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<td>Oral cavity &amp; oropharynx</td>
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<td>Larynx</td>
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Estimated Deaths

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<td>35,000</td>
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<tr>
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<td>6,200</td>
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<tr>
<td>All Sites</td>
<td>155,250</td>
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Leading Cancer in Thailand

1. Breast cancer
2. Trachea/bronchus and lung cancer
3. Colorectal cancer
4. Cervical cancer
5. Liver and intrahepatic bile duct cancer

18.44%
15.58%
13.67%
40.29%
15.14%
7.4%
6.8%
6. Prostate CA 4.96%

Total Top Ten Cancer in Thailand 2013

1. Breast cancer
2. Trachea/bronchus and lung cancer
3. Colorectal cancer
4. Cervical cancer
5. Liver and intrahepatic bile duct cancer
6. Lip and oral cavity cancer
7. Esophageal cancer
8. Non-Hodgkin lymphoma
9. Corpus cancer
10. Nasopharyngeal cancer

Hospital based cancer registry: NCI 2011 (2554)
Hospital based cancer registry: NCI 2013 (2566)
**Growth curve for Cancer**

- **Lethal limit**
- **Limit of detection**
- **Immune system can handle**

**Early Stage VS Late Stage**

**Cancer as a Chronic Disease**

- **Chronic diseases**
  - Shaped by periods of acute and intensive illness followed by periods of remission
- **People with cancer are living for longer with a chronic, but life threatening, illness**
- **Challenges the portrayal/ perception of cancer**
- **Challenges the concept of “palliative” in relation to cancer and its treatment**
- **Concept of the “survivor” having increasing relevance in cancer care**

**Principle of Chemotherapy Uses**

- **Primary modality of treatment**
- **Adjunct treatment**
  - Adjuvant
  - Neoadjuvant
  - Concurrent
- **Palliative treatment**: Palliative chemotherapy
  - Prolong survival: overall, DFS, PFS
  - Improve symptoms, QOL, toxicities

**Concept Palliative Chemotherapy**

- Palliative chemotherapy is given without curative intent, but simply to decrease tumor load and increase life expectancy. For these regimens, a better toxicity profile is generally expected.
- Minimising potential toxicity is the goal
- Try not to compromise on quality of life
- Dose reduction to avoid toxicity is permissible

**The goal of care for a palliative care**

- The patient, who is not benefit from medical treatment aimed at cure and instead the care should be **aimed at managing symptoms and improving quality of life**
- Palliative care patients should **not be subjected to burdensome or futile treatments**

**Objectives in Advanced Disease**

**PERSON:**
- Live longer
- Quality of Life
- Dignity

**STATE:**
- Cost-effectiveness
- Standards of care

**MEDICAL STAFF:**
- Maintain quality of life
- Minimise toxicity
- Prolong survival
- Progression-free survival
- Minimise disease-related toxicity
- Balance between all the various factors
Considerations in Treatment

- Performance Status
- Range of agents
- Therapeutic target
- Measuring benefit
  - Symptoms
  - Radiology
  - Function
- When to break / stop

Palliative in targeted therapy era

Patients usually misled by incomplete or wrong information in the lay media. And dream to the new clinical trial. But, only about 3% of adults with advanced cancer enroll on trials.

Because of:
1. Highly selected cases. “Real-life” patients are typically older and have more comorbidities.
2. In addition, clinical trials are usually conducted only in high-volume and highly experienced centers to ensure rapid accrual of patients.
3. Many new drugs usually give short time of response
4. Mostly, the response is just SD or PR and not CR.

Townsley et al. 2005

What is Palliative Care??

Traditional View

Palliative Care Framework : New

Chemotherapy in metastatic solid tumors

- Palliative chemotherapy is increasingly given near death
- More than 20% of patients receiving Medicare who had metastatic cancer started a new chemotherapy treatment regimen in the 2 weeks before death
- In 2008, a medical director of a large insurance company reported that 1.6% of its cancer patients receive chemotherapy within 14 days of death
- Patients are unlikely to benefit from chemotherapy when they have already been failed by the standard regimens, have poor PS, and otherwise have a poor prognosis
- Survival was significantly longer for hospice patients with lung cancer and pancreatic cancer, marginally longer for colon cancer, but no different with breast or prostate cancer

Lester et al. 2013

JAMA. 2008;299(22):2667-2678
“Early Palliative Care”

- Early palliative care in a broader sense has the capacity to improve the patients’ well-being and survival that may rival oncologic approaches.
- Metastatic lung cancer cases may live longer if they are accompanied by a dedicated team of palliative care specialists parallel to their oncologic treatment.
- Palliative care in this study included:
  - Support to better understand the disease and its treatment.
  - To optimize symptom management by systematically evaluating symptoms.
  - To support decision-making and to help with coping.
  - To make sure that the patient adheres to the rules of treatment (Temel et al. 2010).
- But, this way rarely succeeds in a busy oncological practice hospital oncology ward. So, doing with multidisciplinary team may help in this situation (Okuyama et al. 2011).

Care needs of patients with advanced-stage cancer

1) Cancer management
2) Symptom management and personal care needs
3) The management of comorbidities

Early Palliative Care for Metastatic NSCLC

- Improvements in QOL, depression, and survival.
- Higher quality care at the end of life:
  - Lower rates of IV chemotherapy use.
  - Longer lengths of stay in hospice.

Lung Cancer (NSCLC): Introduction

- Most common stage IV disease.
- Peak age at diagnosis: 50-60 years.
- Pathology: NSCLC (Adenocarcinoma, Squamous, Large cell) vs SCLC.

Hospital based cancer registry: NCI 2010.
NSCLC adenocarcinoma vs squamous cell carcinoma harboring different oncogene aberrations

Adenocarcinoma
- EGFR
- Kras
- ALK/ROS1

Squamous cell carcinoma
- PIK3CA amplification
- PIK3CA mutation
- FGFR1


Lung Cancer (NSCLC): Management

Tumor type: Non-Small Cell vs Small Cell
- Early T1, T2
- Mid-T2
- Late T1, T3, T4

Treatment modalities:
- Surgery
- Chemotherapy
- Radiation
- Combined treatment
- Targeted therapy

No survival different among histological subtypes

Development in Treatment of Advanced NSCLC (Personalized Treatment)

- EGFR TKIs in EGFR mutation-positive disease: > 24 months
- Platinum singlet 6-8 months
- Platinum doublet 8-10 months
- Bevacizumab + platinum doublet 12.3 months
- Cisplatin + carboplatin 2-5 months

All recent randomized studies have similar results. No clear efficacy benefit for non-platinum combinations or triplet combinations. A paradigm shift is needed!!

Survival by Treatment Group

Response Rate 25-35%, Median TTP 4-6 Months
Median Survival 8-10 Months, 1-yr OS 30-40%

No survival different among histological subtypes

Schiller JH, et al., NEJM January 2002

No survival different among histological subtypes

Survival Time (months)

Overall survival

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Personalized Therapy for NSCLC

**EGFR Timeline**
- EGFR mutations identified in NSCLC
  - 1990s: 2004-2006
  - 2009
- Axitinib approved for NSCLC
- Osimertinib approved for EGFR mutation NSCLC

**ALK Timeline**
- ALK discovered
- Responses seen in ALK+ NSCLC treated with crizotinib or chemotherapy
- ALK+ NSCLC discovered in 2007
- ALK+ NSCLC approved for ALK+ NSCLC

**NSCLC : NCCN Guideline 4.2016**

**SOMATIC THERAPY FOR NSCLC DISEASE**
- NCCN Guidelines Clinical Practice Guidelines in Oncology

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- NCCN Guidelines Clinical Practice Guidelines in Oncology

**Colorectal Cancer : Introduction**

**Peak age at diagnosis**: 50-60 years

**hospital based cancer registry: NCI 2010**

**Advanced stage**: 37%

**Early stage (Stage I-III)**: 63%

**Sporadic**

**Hereditary**

**Hereditary cancer variants**
- Familial CRC of syndrome "X" (FAP, AFAP, MTAP)
- Constitutional mosaic playonin (MLPA)
- Mixed Polyposis Syndrome (MPS)
- TGFBR1
- TGFBR2
- GNAS
- CDH1
- SMAD4

**Sporadic**

**Heterogeneity**
- AC-1 without MMR
- Constitutional mosaic playonin (MLPA)
- TGFBR1
- TGFBR2
- GNAS
- CDH1
- SMAD4

**Colorectal Cancer : Introduction**

**Hospital based cancer registry: NCI 2010**
Colorectal Cancer: Pathogenesis

Adenoma-Carcinoma process (7-10 yrs)
Risk factor for cancer ex: High-grade dysplasia, >10 mm in size, Villous component, Number ≥3

Colorectal Cancer: Clinical

- Proximal colon (Right-sided)
  - Polypoid or fungating exophytic mass
  - Without obstructive symptoms or alterations in bowel habits
  - Occult bleeding

- Distal colon (Left-sided)
  - Annular or encircling lesions: “apple-core” or “napkin-ring”
  - Symptoms of bowel dysfunction (constipation, diarrhea, bowel habit changes or bowel obstruction)

Treatment Evolution in mCRC and Impact on Median Survival

<table>
<thead>
<tr>
<th>No chemotherapy</th>
<th>5-FU monotherapy</th>
<th>Combination chemotherapy</th>
<th>Combination chemotherapy + targeted agents</th>
<th>First/second-line sequencing</th>
<th>Ongoing studies</th>
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<tbody>
<tr>
<td>4.4 months</td>
<td>11.3 months</td>
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<td>13.2 months</td>
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<td>17.4 months</td>
<td>24.3 months</td>
<td>21.5 months</td>
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</table>

Colorectal Cancer: Systemic treatment

- Adjuvant treatment
  - 5FU/LV
  - Capecitabine
  - Oxaliplatin combination
    - FOLFOX
    - FLOX
    - XELOX

- Metastatic treatment
  - 5FU/LV
  - Capecitabine
  - Oxaliplatin combination
  - Irinotecan combination
  - Adding Targeted Rx
    - Bevacizumab
  - Cetuximab/Panitumumab
  - Avastin (VEGF trap)
  - Regorafenib
  - TAS-102

The integration of biologicals in the continuum of care of CRC

1st line cytotoxic 2nd line cytotoxic 3rd line cytotoxic

How to start? How to select?
At progression change chemotherapeutic or both?

Independent sequences?

1st biologic 2nd biologic
Breast Cancer: Introduction

- 20% of pts initially diagnosed with regional stage disease will develop MBC
- Approximately 6% of breast cancers are metastatic at diagnosis with a 5-year survival rate of 21%

Stage and breast cancer

Early BC (stage I-II) 63.8%
Locally advanced BC (stage III) 23.9%
Advanced BC 8.6%

Hospital based cancer registry: NCI 2011

Breast Cancer Up Until Now: Diagnosis
Testing for 1 or 2 Specific Molecules

- Estrogen Receptor: 75% of breast cancers are ER+
- HER-2: 20-25% of breast cancers are HER-2+

Histopathology  
IHC expression  
Gene expression profiling

Molecular Classification breast cancer

Breast cancer is not one disease
But a group of biologically distinct diseases

5 subtypes:
- Luminal A
- Luminal B
- Basal like
- HER2 positive
- normal-like
### Molecular Subtype Breast Cancer and Prognosis

**Overall Survival**
- Lum A, Lum B, Lum C, normal-like, Basal, HER2

**Breast Cancer - Risk Free Survival**
- Lum A, Lum B, normal-like, Basal, HER2

Sorlie et al. PNAS 2001

- **Molecular Subtype**
  - Breast Cancer

- **Prognosis**
  - Lum A, Lum B, normal-like, Basal, HER2

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### Breast Cancer: Treatment

**Multidisciplinary team for breast cancer**
- Radiologist
- Pathologist
- Breast cancer surgeon
- Radiation oncologist
- Medical oncologist

**Treatment**
- **Local treatment**
  - Surgery
  - Radiation therapy

- **Systemic treatment**
  - Chemotherapy
  - Endocrine or hormone therapy
  - Targeted therapy

---

### NCCN guideline Version 2.2016

**Premenopausal patients**
- Ovarian ablation/suppression then follow postmenopausal guidelines

**Postmenopausal patients**
- Nonsteroidal AI
- Steroidal AI
- Exemestane+everolimus*
- Fulvestrant*
- Tamoxifen or toremifene
- Megestrol acetate
- Fluoxymesterone
- Ethinyl estradiol

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### Breast Cancer: Historic Timeline of Therapies for HR+ subtype

- **1980s**
  - Anthracyclines
  - Tamoxifen
  - Others

- **1990s**
  - Taxanes
  - ERDs
  - Targeting mechanisms of endocrine resistance

- **2000s**
  - Capecitabine
  - Osimertinib
  - Erlotinib

- **2012**
  - EGFR antibodies

### Breast Cancer: HER2 positive subtype

**ASCO/CEP HER2 testing guideline:**
- NCCN Breast Cancer Guideline: 1.2015
Breast Cancer: anti HER2 Therapy

Drugs that approved by FDA
- First-generation: Trastuzumab (Ab)
- Lapatinib: oral TKI
- Pertuzumab (Ab)
- T-DM1 (Antibody conjugated CMT)
- Neratinib

Breast Cancer: Rx in HER2+ subtype

Adjuvant/neoadjuvant Rx

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<tr>
<th>Regimens</th>
<th>Preferred agents</th>
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Duration: 1 year

Metastasis Rx

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</table>

Duration: Treatment until PD or toxicity (1 year)

Palliative Chemotherapy: Summary

- Palliative chemotherapy aims at managing symptoms, improving quality of life and minimise disease-related toxicity
- Patients are unlikely to benefit from chemotherapy when they have already been failed by the standard regimens, have poor PS, and otherwise have a poor prognosis
- Combined standard oncology care and palliative care should be considered early in the course of illness for any patient with metastatic cancer and/or high symptom burden

Q and A Session

Thank you for your attention