Best Supportive Care: Integration into Clinical Trials

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Outline

• Goals of palliative chemotherapy
• Trial End points
• Defining the intervention
• Trial Design
• Recruitment Issues
Outline

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• Trial End points

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• Recruitment Issues
Goals of Palliative Cytotoxic Therapy

• Selfless goals
  – Drug evaluation
  – Other patients and future trials

• Selfish goals
  – Shrink tumor (RR)
  – Slow growth and prolong life (PFS)
  – Extend survival (OS)
  – Temporarily relieve symptoms (QOL)
Palliative Therapy: Considerations

• **When is it appropriate?**
  – Response rates (does RR=decreased symptoms?)
  – Predictors of response (Moore)
  – Life Gained/Cost (2-3 mos)
    • Do we help them live better?

• **Explaining the Risk: Benefit Ratio**
  – Describing side effects and symptoms
  – Prognostication
  – Communicating for fully informed consent
    • Does she really know the risks/benefits

» Penson RT Lancet Oncol. 2015 Mar;16(3):301-11
More “life” at what cost?

**Ovarian Cancer Platinum Resistant**
- BSC was the only definitive cost-effective treatment
- Second-line monotherapy also cost-effective strategy
- Second-line combination therapy and third-line therapies-unfavorable ICER
  - Rocconi RP et al Cancer. 2006 Aug 1;107(3):536-43

**Ovarian Cancer Platinum Sensitive**
- Second-line chemotherapy is cost-effective
- Third- and fourth-line chemotherapy are not cost-effective

**Terminal Cervix Cancer Cost-effectiveness model**
- Single agent chemotherapy + home hospice (3) and selective chemotherapy (2) are cost effective
- Cisplatin based doublet chemotherapy (1) was not cost effective (?)
  - Phippen, et al. Gynecol Oncol 130, 2013
Risks of prescribing palliative chemotherapy

Chemotherapy Side effects-detriment to QOL
  - Shorten life (?sepsis/perforation)
  - Fatigue, neuropathy

Effect on daily living
  - More trips to hospitals, interventions, x-rays, IVs
  - Resource allocation (person, family, community, country)

Lost EOL planning
  - Delay in preparations for end of life
  - Limiting hospice opportunities
  - Resource allocation (person, family, community, country)
  - Opportunities to have meaningful legacies and final visits

Unmeasured effects??
Time for Different End Points?

• Decreased size of tumor does not necessarily equal improved QOL/Symptoms
  – Dual Endpoints Necessary

• Specific Aspects of QOL
  – Physical, PS
  – Social
  – Functional (ADLs)
  – Psychological (HADS)
  – Customized symptoms (ESAS)
  – Pain (BPS)
  – PROs
  – More Existential
Why not dual targets?
RR & Symptoms/Well being

• High Physical Well-Being domain of FACTCX was the only predictor of improved OS (p<0.001)
  – Chase DM Gynecol Oncol 2012; 125: 315-319

• Worsening physical symptoms and low physical functioning correlated with decreased OS

• Theoretically, improved QOL is tied to drug efficacy but is it due to something else?
Palliative Care Improves Outcomes

• **QOL**
  - Higginson IJ Cancer J 2010; 16; 423-435
  - Bakitas M JAMA 2009; 302: 741-49
  - El-Jawahri A J Support Oncol 2011; 9; 87-94

• **Survival**
  - Temel JS N Engl J Med 2010; 363; 733-42
  - Add most recent JCO
Multiple Potential Targets to Improve

Physical symptoms

Obstruction, nausea, diarrhea, constipation, lymphedema, bleeding, pain, GU obstruction, fistulas, DVT, dyspnea, odor, fatigue, sexuality,

Psychological Distress

Anxiety, depression, spiritual, dignity, financial distress, abandonment, guilt, forgiveness, caregiver, family, children, suicide
Symptoms of Ovarian Cancer in last 6 months of life
Herrinton et al J Pain and Symptom Management 2007;34:237

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Percentage of Patients</th>
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<tbody>
<tr>
<td>Fatigue and Weakness</td>
<td>75%</td>
</tr>
<tr>
<td>Nausea and Vomiting</td>
<td>71%</td>
</tr>
<tr>
<td>Constipation</td>
<td>49%</td>
</tr>
<tr>
<td>Edema of limbs</td>
<td>44%</td>
</tr>
<tr>
<td>Anemia</td>
<td>34%</td>
</tr>
<tr>
<td>Ascites</td>
<td>28%</td>
</tr>
<tr>
<td>Bowel Obstruction</td>
<td>12%</td>
</tr>
</tbody>
</table>
Performance Status and Symptom Scores of Women With Gynecologic Cancer at EOL

Trajectory in last 6 months of life.

**Drowsiness, decreased well-being, lack of appetite, and tiredness** increased in severity closer to death
Prevalent in more than 70% of patients in the last week of life

Patients with **cervical cancer** had increased odds of moderate to severe **pain** (1.74; 95% confidence interval, 1.30-2.32) compared with ovarian cancer.

• Pain is the primary complaint for pts with advanced or recurrent CCx at time of referral to SCC

• AND more than half are significantly burdened with fatigue, loss of appetite, difficulty with sleep and lack of well-being.

  » Ramondetta LM et al SGO 2015
Outline

• Goals of palliative chemotherapy

• Trial End points

• Defining the intervention

• Trial Design

• Recruitment Issues
WHO Definition of Palliative Care

Palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual. Palliative care:

• provides relief from pain and other distressing symptoms;
• affirms life and regards dying as a normal process;
• intends neither to hasten or postpone death;
• integrates the psychological and spiritual aspects of patient care;
• offers a support system to help patients live as actively as possible until death;
• offers a support system to help family cope during pts illness and their own bereavement;
• uses a team approach to address the needs of patients and their families, including bereavement counseling, if indicated;
• will enhance quality of life, and may also positively influence the course of illness;

is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy / radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications.

Evidence based guidelines exist

– ESMO.org
– NCCN.org
– ASCO.org
Both visits included discussions about symptoms and illness status. Oncologic visits focused on treatment and medical complications. PC visits emphasized symptoms and psychosocial elements.

1. Relationship and rapport building
2. Addressing symptoms
3. Addressing coping
4. Establishing illness understanding
5. Discussing cancer treatments
6. End-of-life (EOL) planning
7. Engaging family members

Yoong...Temel et al JAMA Intern Med 2013.1874
BSC in Clinical Trials

- Clinicaltrials.gov (>200 active trials with BSC arm)
  - Testing of new targeted agents vs BSC
  - None are in Gyn Tumors

- However—almost all lack definition
  - Examples—“measures designed to provide palliation of symptoms and improve quality of life as much as possible”

- Thus—lack of clinically useful information
  - Over or underestimate value of new agent
  - Cost often not included health care
  - Effect—ethical imperative—on patients EOL
BSC in Clinical Trial Review

Prior panel defined 4 key domains

- Multidisciplinary care
- Supportive care documentation
- Symptom assessment as often as the intervention or more
- Guideline based symptom management

Databases searched 2002-2012

- Trials conformed to <18% of consensus based BSC standards
- 35% had detailed description of bsc
- 65% reported baseline and regular symptom assessment
- 47% reported using validated symptom assessment measure
- 35% reported symptom assessment at identical intervals in experimental and BSC arms
- None listed an evidence based guideline for symptom management
- None reported standardization of bsc across sites
- Non reported educating pts on symptom management or goals of anti cancer therapy
- Non reported offering access to pc specialists sw and financial or spiritual counseling

— Cherney NL J Clin Oncol. 2009 Nov 10;27(32):5476-86
Supportive care and BSC interventions in Trials Enrolling Pts with Cancer

- Literature review 1980-2012
- Systemic vs SC compared to WHO guidelines (recommend palliative care therapies integrated into care)
- 189 articles, 73 met inclusion
- 75% had some definition of SC
  - Half of these defined as “at the discretion of the treating physician” without standardization
  - Two studies incorporated physical, psychological and social assessments including referral to Pall Care specialists
  - BSC more likely to use Tfx, abx but less likely to include steroids, pall care specialists than SC trials
- 66% used term BSC
Lack of Definition: Lack of Clinically Meaningful Results

• **Patients in same trial get different care**
  – Different effects on QOL and OS
  – Risk to internal validity

• **Study replication**
  – Inconsistency in application of interventions
  – Risk to external validity

- Cherney NL. J Clin Oncol. 2009 Nov 10;27(32):5476-86
BSC Examples

• Erlotinib or BSC for third-line treatment of advanced lung cancer
  – Control group received BSC
  – BSC defined as all treatment received within the health care system from end of second-line treatment to death or censoring
    • Ian Cromwell et al Lung Cancer 76 (2012) 472-477

• Premetrexed +BSC vs BSC mesothelioma
  – Treatment administered with intent to maximize QOL without a specific antineoplastic regimen including antibiotics, analgesics, antiemetic, thoracentesis, pleurodesis, blood transfusions, nutritional support and XRT for pain, cough, dyspnea or hemoptysis

• Panitumumab +BSC vs BSC chemo refractory colorectal cancer
  – The best palliative care per investigator excluding antineoplastic agents
  – Listing including analgesics, antibiotics, blood transfusions, steroids, antiemetics, anti diarrheal, or vitamins
    • Cutsem doi: 10.1200/JCO.2006.08.1620 JCO May 1, 2007 vol. 25 no. 13 1658-1664
More Examples

• LUCEOR: lung ca economics and outcomes research study
  – 10 countries-1327 pt charts
  – BSC categories defined by attending physician
    • Narcotic/non narcotic analgesics
    • Corticosteroids and GI medication
    • 24 categories-no where did it mention EOL planning
      – Lester JF Lung Cancer 82(2013) 128-135

• Gefitinib + BSC in refractory advanced lung cancer: RPCT
  – All patients received BSC according to the local practice of the individual institutions
    • Nick Thatcher, et al Lancet 2005; 366; 1527-37

• RCT: Docetaxel vs BSC in NSLC
  – BSC arm “treated with whichever therapy was judged to be appropriate by the treating physician. This treatment could have included treatment with antibiotics, analgesic drugs, transfusions, and palliative radiotherapy”
    – TTP 10.6 vs 6.7 weeks (MS 7 vs 4.6 mo)
      • Shepherd FA JCO Vol 18 No 10 2000 pp 2095-2103

• Maintenance pemetrexed + BSC vs placebo + BSC in lung cancer RPCT
  – BSC definition not even mentioned
    • Tudor Ciuleanu, Lancet 2009; 374: 1432–40
Strict quality control measures for BSC - implemented and monitored.

- All patients received standard BSC regimen defined in study
  - BSC – multi-professional attention to overall physical, psychosocial, spiritual, and cultural needs available at all stages of illness.
  - Included, but not restricted to, analgesics, paracentesis, psychosocial care, nutritional support, and blood transfusion.
  - Localized radiotherapy to alleviate pain was allowed, provided that the dose in palliative range.
  - Investigators free to provide nonprotocol supportive care measures at any time if felt to be in patient’s best interest.

- BSC patients could exit BSC and were allowed to receive chemotherapy.

- Median OS 5.3 mos in SLC arm and 3.8 mos in BSC arm
ENABLE

- **Educate, Nurture, Advise, Before Life Ends**
  - Telehealth early PC model designed for rural populations

- **PC Intervention**
  - In person PC consultation, structured PC telehealth nurse 30-45 min coaching sessions (1q wkh6), monthly follow up
    - Coaching by APN on problem solving, Symptom management, self care, identification of resources, communication, decision making, ACP, life review
    - Includes 3 session life review

- **ENABLE II RCT (n=322)**
  - Intervention c/w usual cancer care (oncologist & sc specialists whenever requested)
  - Intervention group with higher scores for quality of life and mood, but did not have improvements in symptom intensity scores or reduced days in the hospital or ICU or emergency department visits
ENABLE II RCT Burdon vs Benefit

• Benefits described by patients
  – Enhanced problem solving skills
  – Better coping
  – Feeling empowered
  – Feeling supportive/reassured

• Themes as to why they participated
  – Helping future patients
  – Contributing to science
  – Gaining insight through completion of questionnaires
  – Trial interventions aspects to improve
ENABLE III Outcomes—Early vs Late

• RCT
  – Early (within 30-60 d from enrollment) vs Delayed PC (3 mos later)
  – At diagnosis, recurrence, progression, consent obtained median 28 days after

  – Effect on QOL, Symptom impact, mood, 1 yr survival, resource use (ICU, admit, ER, chemo last 14 days, location of death)

• PROs not different
• 1 yr survival E 63% vs L 48% (p=.038)
• Resource rates similar
  – Hospital days
  – ICU
  – ER
  – Home death
  – Last 14 days chemo
    • Bakitas MA et al J Clin Oncol
ENABLE III limitations/questions

- Reduced sample size (type II error in PROS)?
- 3 mos delay not long enough to see benefits?
  - Distress levels were low at 3 mos?
- Survival benefits may be from unmeasured PC effects-essential elements?
- Measurement device not sensitive enough?
  - QUAL-E symptom impact subscale
- Diluted impact: 50% in delayed group referred early
- Personnel?
Consensus Definition-Evidence Based Supportive Care

Highest scored components

- Symptom management
- Baseline & follow up assessment
  - validated instruments
- Symptom assessment intervals same in groups
- Evidence based guidelines for symptom management (NCCN, ESMO)
- Documentation of supportive care interventions
- Access to palliative care specialists
- Communication of goals of care
  - Zafar S Y...AP Abernethy   Lancet Vol 13 2012
Derived Standards for BSC Clinical Studies

Adequate supportive and palliative care staff training for primary

Interdisciplinary care with a minimum team of physician, nurse, and social worker

Care coordinated to minimize the burden on patients, the caregiver or caregivers, and family

Routine evaluation-prevalence/severity of physical/psychological symptoms and social supports — Validated tools

Treatment of physical symptoms/pain with evidence-based approaches and validated care pathways Monitoring for the adequacy of relief and adjustment strategies as necessary

Cherny et al JCO November 10, 2009 vol. 27 no. 32 5476-5486
Derived Standards for BSC Clinical Studies

Access to specialist palliative or pain-management when needed

Meticulous management of the adverse effects of treatment

Availability of psychological and spiritual care for patients and their family members

Ongoing care planning, based upon ongoing assessment, determined by goals set with pt and family

Cherny et al JCO November 10, 2009 vol. 27 no. 32 5476-5486
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Two designs of best supportive care studies.

<table>
<thead>
<tr>
<th>Design</th>
<th>SC</th>
<th>Blinding</th>
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<tbody>
<tr>
<td>Treatment vs SC</td>
<td>1 arm</td>
<td>Unblinded</td>
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<tr>
<td>Treatment</td>
<td></td>
<td></td>
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<tr>
<td>Incurable cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment +SC vs SC alone</td>
<td>2 arms</td>
<td>Unblinded Can be placebo blinded</td>
</tr>
<tr>
<td>Incurable cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SC + treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SC +/- placebo</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Nathan I. Cherny et al. JCO 2009;27:5476-5486
BSC incorporated in Study Design

Randomized Phase II vs Phase III
- Treatment vs BSC (ethics?)
- Treatment +/- BSC (ethics?)

- Treatment + BSC vs Placebo +BSC
- Cross over
Intervention Documentation

Example - Intervention “Hycamtin”

- Dose, interval, infusion, duration, dose intensity and reason for discontinuation all documented

- If interventions not described or documented
  - Drug effect inflated (type 1)
  - Drug effect underreported (type 2)
Clinical Trial Design: Dual End Points

• Traditional End points
  – OS
  – PFS
  – PR/CR/SD
  – QOL

• Dual Endpoint with Symptom Control
  – Anxiety and Depression
  – Specific Symptom targeting

• Cost effective analysis
Symptom Assessment

• Intervals identical
• High quality assessment (validated scales)
• All inclusive assessment

• CTCAE (common terminology criteria for adverse events)
  – Doesn’t clearly differentiate between intervention/cancer symptoms
  – Important to include patient reported outcome measures (PRO)
    • Assess QOL, symptom intensity and symptom burden including effect on activities of daily living (being developed-PRO-CTCAC-Cleeland)
Validated assessment scales

- Distress thermometer
- ESAS, EORTIC
- HADS
- MDASI
- Mini mental
- Brief Pain Inventory
- FACT O,Cx,U
- Cost
- PRO
Best Supportive Care for All Patients?

• Different needs
  – Target those most at risk for lack of response to cytotoxic treatment
    • Moore criteria cervix
    • Platinum resistant ovarian
    • Clear cell
  – Individualize for
    • Culture, age, geography
    • Coping
    • Vulnerable populations
    • Self manage/social support
    • Access
Outline

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The complexity of decisions lies both in the **beliefs and presentation** of the situation by the physician as well as the hopes and beliefs of the patient.
Patients' expectations- willingness

69% of pts with lung cancer and 81% with colorectal cancer did not report understanding that chemotherapy was not at all likely to cure their cancer.

The risk of reporting inaccurate beliefs was higher
1-among nonwhite and Hispanic patients
2-among pts who rated communication with their physician very favorably

Educational level, functional status, and the patient's role in decision making were not associated

Effect of a Beta Adrenergic Blockade combined with Relaxation/Guided Imagery Audio Intervention on Symptom Distress in Women with Advanced, Recurrent Incurable Cervical Cancer-Feasibility study: MP3 Trial

**Primary Objectives:**
Determine the proportion of pts of completing symptom inventory, anxiety and depression survey, pain inventory, and quality of life surveys (MDASI, HADS, BPI, FACTcx)

Determine the proportion of pts of completing combined intervention of twice daily beta blocker use and twice weekly relaxation and guided imagery (R/GI) at 2 time points (2 and 4 mos)

**Secondary Objectives:**
Index cervix ca specific symptomatology in this population and the serial change over intervention.

Determine the impact of beta blocker and PMR/GI on symptoms, anxiety and depression, pain, and quality of life (MDASI, HADS, BPI, FACTcx)

**Exploratory objectives:**
Measure changes in serum levels of IL-6, IL-8, IL-10 and VEGF, CRP during treatment with propranolol in addition to receiving PMR intervention

Measure change in basal metabolic rate on propranolol

To measure HPV components (e.g. E6 or E7) in circulating cell-free DNA during intervention
BB Cervix – closed due to low accrual

Reasons for ineligible

<table>
<thead>
<tr>
<th>Reason</th>
<th>Count</th>
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</thead>
<tbody>
<tr>
<td>Taking BB</td>
<td>3</td>
</tr>
<tr>
<td>BP too low/cardiologist recommended against</td>
<td>5</td>
</tr>
<tr>
<td>Pulse too low</td>
<td>1</td>
</tr>
<tr>
<td>Didn't want any more pills/treatment/sent to hospice</td>
<td>4</td>
</tr>
<tr>
<td>No disease seen</td>
<td>5</td>
</tr>
<tr>
<td>No show</td>
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</tr>
<tr>
<td>Steroid use</td>
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<tr>
<td><strong>Preferred chemotherapy</strong></td>
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<td>No English/Spanish language</td>
<td>4</td>
</tr>
<tr>
<td>Not being treated at MDACC</td>
<td>4</td>
</tr>
<tr>
<td>No reason given-not interested</td>
<td>1</td>
</tr>
<tr>
<td>Vulva/brain met</td>
<td>2</td>
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</tbody>
</table>
Recruitment for PC trials

• Ethical issues
  – Burden, intrusive
  – Self reports (fatigue/reminder of illness)
  – Concerns on randomization
  – Concern by clinician or carers
  – Vulnerable population
  – Reduced cognitive ability of potential participants
  – Potential for need for emergency treatment

• Logistical issues
  – Funding, research infrastructures
  – Deterioration and death
  – Travel
  – Effective dissemination of trial information and raisin recruitment willingness among potential participants and recruiting staff.

• But qualitative study shows more benefit than burden

  Jordhoy MS Palliat Med 1999 13 299-310
  Cook AM Palliat Med 2002 16 163-165
  Boland J et al J Pain and Symptom Management Vol 49 (4) 2015
BSC in the Community

• Capacity-team in place
  – Specialists (nurses, docs, chaplain, psych, social workers) but even one or ? Teletherapy?
  – Medications (pain, GI, psych)
  – Physical location-sending home...to where
  – Children of patients

• Limited resources (EG placebo in chemo unit)

• Needs of individual institutions
Effective dissemination of trial information and recruitment willingness

RCTs
- Easy to read info vs standard consent didn’t accrual rate $p=0.21$
- Educational video for patients didn’t increase enrollment $p=0.19$
- Audiovisual info +/- standard trial info did not help $p=0.66$
- Study specific newspaper articles did not help
- Targeted info in potential recruiting sites for institution-NS
  - Teaching within the institution
  - Face to face site visit vs phone with coordinating group
  - Augmented communication from coordinating trial center

- Boland J et al J Pain and Symptom Management Vol 49 (4) 2015
BUY IN?

The patient /location

• “efficient study specific advertising strategies should be developed and take into account knowledge of patient flow through the service at any recruiting site”

The staff

• Education didn’t help
• However, In a palliative care prognostication study, gatekeeping by clinical staff accounted for 24% of inaccessibility”
• Direct contact with the physicians may help

— Boland J et al J Pain and Symptom Management Vol 49 (4) 2015
— Stone PN et al BMJ Support Palliat Care 2013; 3;318-323
Proposed Concept
Recurrent Cervical Cancer
1-2 prior systemic therapies

Best Supportive care

Best Supportive Care Plus
227 Queue enrollment OR
Cytotoxic of choice
CVM 1402 Proposal
Study Design

• Novel design
  – patients may be enrolled on a 227 Queue trial or given chemotherapy at the choice of the investigator

• Moore criteria
  – Used for stratification
  – May be dropped if not predictive from GOG 240

• Cross over ? At two months

• Projected Sample size
  – 110 patients to allow for dropout
  – Attrition for death, symptom burden–(26% Primary End Point, 44% by end of study in meta analysis of SC trials)
    • Hui D Cancer 2013; 119  1098-1105
Study Objectives

• Primary Objective
  – To determine if the addition of cytotoxic or targeted therapy to best supportive care in patients with recurrent cervical cancer following prior chemotherapy improves overall survival

• Secondary Objective
  – To determine if the addition of cytotoxic or targeted therapy to best supportive care in patients with recurrent cervical cancer following prior chemotherapy improves progression–free survival
Study Objectives

• Tertiary Objective
  – To determine the impact on quality of life (or symptom-pain) that cytotoxic or targeted chemotherapy and best supportive care has compared to best supportive care alone
  – To record symptoms of patients with advanced cervical cancer
  – To evaluate PROs
  – To compare symptoms using ESAS and FACT Cx

• Exploratory Objective
  – To compare baseline QOL scores using the FACT Cx to predict outcome regardless of treatment assignment
What would you want to do with a “known precious quantity of time?”

What could we accomplish for people if we designed our trials accordingly?
Gynecologic Oncology Community
Focus : Primum non nocere

1. Improving QOL using supportive care strategies should be the minimum “therapeutic” goal for women with incurable cancer.

2. Decisions to proceed with palliative chemotherapy should be based on medical knowledge of predictors of response and honest conflict-free disclosure of response rates and survival estimates.

3. Include detailed information regarding side effects and in most cases include a recommendation to forgo second- or third-line chemotherapy unless in the setting of a well designed clinical trial (?)
4. Improving identification of predictors of response to therapy and incorporating the identified factors into decision aids

5. Trial design should include molecular targeting AND supportive care objectives (reducing pain, anxiety, depression, cachexia, and fatigue)

6. Think beyond standard trial outcomes...
Endpoints in years, months, weeks gained...
Will we soon report in **days & hours**?

Isn’t it about time you started thinking outside the box?