Survivorship Issues After Chemotherapy in Metastatic/Recurrent Endometrial Cancer

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First-Line Chemotherapy

- Cisplatin
- Doxorubicin
- Paclitaxel
- Carboplatin
- Paclitaxel
GOG 209

Randomization to Regimen I requires determination of LVEF. LVEF ≥50% receive treatment per Regimen I. LVEF <50% crossover to Regimen II.

**Regimen I**
- Doxorubicin
  - 45 mg/m² IV day 1
- Cisplatin
  - 50 mg/m² day 1
- Paclitaxel
  - 3 hr 160 mg/m² day 2
- G-CSF*
  - Repeated every 21 days for 7 cycles

**Regimen II**
- Paclitaxel
  - 3 hr 175 mg/m² day 1
- Carboplatin
  - AUC 6 IV day 1
  - Repeated every 21 days for 7 cycles

* Filgrastim (G-CSF, Neupogen) 5 mcg/kg days 3-12 or Pegfilgrastim (G-CSF) 6 mg Day 3.
  - Japanese institutions will use 2 mcg/kg/day dosing.

** See section 5.2211 for initial reduced starting doses for prior radiation therapy.

Activated  8/25/03
Revised  3/15/04, 5/2/05, 8/29/05, 11/21/05, 4/17/06, 10/30/06, 3/26/07, 2/11/08, 7/28/08, 4/12/10
Closed  4/20/09
Toxicity

- TAP vs. TC
  - Neutropenic fever:
    - 7% vs. 6%
  - Sensory neuropathy > G1:
    - 26% vs. 19% (p<.01)

Miller et al. Presented at 2012 SGO Annual Meeting
Survival
By Randomized Treatment

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Alive</th>
<th>Dead</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAP</td>
<td>299</td>
<td>343</td>
<td>642</td>
</tr>
<tr>
<td>TC</td>
<td>295</td>
<td>368</td>
<td>663</td>
</tr>
</tbody>
</table>

Proportion Surviving

Months on Study

Figure 1

Miller et al. Presented at 2012 SGO Annual Meeting
Conclusions

- TC is not inferior to TAP in terms of PFS and OS based on interim analysis results
- Overall, the toxicity profile favors TC
- Thus, TC as prescribed in this study is an acceptable backbone for further trials in combination with "targeted" therapies

Miller et al.  Presented at 2012 SGO Annual Meeting
Second- or Later Line Treatment

- Paclitaxel
- Bevacizumab
- Ifosfamide
- Ixabepilone
- Docetaxel
- Topotecan
- Oxaliplatin
- Etoposide
- Pegylated liposomal doxorubicin
# Third Line or Later Treatment

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Schedule</th>
<th>N</th>
<th>ORR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel</td>
<td>175 mg/m²</td>
<td>Every 21 days</td>
<td>48</td>
<td>25</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>15 mg/kg</td>
<td>Every 21 days</td>
<td>53</td>
<td>15</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>1.2 g/m²/day</td>
<td>5 days/4 weeks</td>
<td>52</td>
<td>15</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>36 mg/m²</td>
<td>Days 1,8,15/4 weeks</td>
<td>27</td>
<td>7.7</td>
</tr>
<tr>
<td>Topotecan</td>
<td>1.0 mg/m²</td>
<td>Days 1-5/4 weeks</td>
<td>53</td>
<td>15</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>130 mg/m²</td>
<td>Every 21 days</td>
<td>50</td>
<td>14</td>
</tr>
<tr>
<td>Ixabepilone</td>
<td>40 mg/m²</td>
<td>Every 21 days</td>
<td>50</td>
<td>12</td>
</tr>
<tr>
<td>Etoposide</td>
<td>50 mg</td>
<td>Days 1-21/4 weeks</td>
<td>44</td>
<td>14</td>
</tr>
<tr>
<td>PLD</td>
<td>50 mg/m²</td>
<td>Every 28 days</td>
<td>46</td>
<td>9.5</td>
</tr>
</tbody>
</table>
## Third Line or Later Treatment

<table>
<thead>
<tr>
<th>Agent</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel</td>
<td>Neuropathy, alopecia, neutropenia</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>HTN</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>Neutropenia, neuropathy</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>Neutropenia, GI, neuropathy</td>
</tr>
<tr>
<td>Topotecan</td>
<td>Hematologic, GI</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>N/V, neurotoxicity</td>
</tr>
<tr>
<td>Ixabepilone</td>
<td>Neutropenia, GI, neurologic, infection</td>
</tr>
<tr>
<td>Etoposide</td>
<td>Neutropenia, N/V, anemia</td>
</tr>
<tr>
<td>PLD</td>
<td>HFS, mucositis</td>
</tr>
</tbody>
</table>
GOG 86P

- Phase II randomized trial
  - Carboplatin + Paclitaxel + Bevacizumab
  - Carboplatin + Paclitaxel + Temsirolimus
  - Carboplatin + Paclitaxel + Ixabepilone
Cancer Survivors

- ASCO definition

Patients who may be in *remission*, those for whom cancer has become a *chronic disease*, and those who are *cured*

Estimated Number of Cancer Survivors in US

Age Distribution of Cancer Survivors

Endometrial Cancer

- Estimated 600,346 women who are endometrial cancer survivors in the US
- Lack of clear evidence for what constitutes best practices in caring for these patients

http://cancercontrol.cancer.gov/ocs/prevalence
Effect of Cancer and Its Treatment

- 50% of survivors may suffer from late effects of cancer tx
- Most common are depression, pain, fatigue
- Prevalence may be increasing
  - More intense and complex tx
    - Surgery, RTX, chemotherapy, hormone tx, targeted biologics

Hewitt et al. IOM Research Council 2006
IOM
Cancer Patient to Cancer Survivor: Lost in Translation

- Essential components of survivorship
  - Prevention of new/recurrent cancers
  - Surveillance for cancer spread, recurrence or second cancers
  - Assessment of late psychosocial and medical effects
  - Intervention for consequences of cancer and tx
  - Coordination of care between PCP and specialists

Hewitt et al. IOM Research Council 2006
NCCN Guidelines for Survivorship

- Anxiety and depression
- Cognitive decline
- Pain
- Sexual dysfunction
- Immunizations and prevention of infections
- Fatigue
- Sleep disorder
- Exercise

NCCN Guidelines Version 1.2013 Survivorship
Anxiety and Depression

- May affect up to 29% of survivors
- 19% of survivors may meet criteria for post-traumatic stress disorder
- Fear of recurrence
- From physical compromise, social isolation, work, financial problems

Smith et al. J Clin Oncol 2008;26:934
Management

- Screening especially at times of transition, surveillance, significant loss, major life events, isolation
- Exercise
- Supportive psychotherapy
- Cognitive behavioral therapy
- Medical therapy

Smith et al. J Clin Oncol 2008;26:934
Cognitive Dysfunction

- May be related to CNS/brain involvement, chemotx, RTx, hormone tx
- Incidence ranges from 19-78%
- Affected domains include
  - Executive function
  - Learning
  - Memory
  - Processing speed
- Mechanism
  - Elevated cytokine levels
  - DNA damage
  - Damage to white matter
  - Fatigue, depression

Management

- Self-management/coping strategies
  - Planners, minimize distractions, avoid multi-tasking
- Tx fatigue and sleep disturbances
- Relaxation/stress management
- Routine exercise
- Occupational therapy
- Pharmacologic interventions

Pain

- Approximately 33% of cancer survivors experience chronic pain
- May result in psychosocial distress and poor QoL
- Barriers to optimal care
  - Lack of training of HC providers
  - Fears of side effects/addiction
  - Reimbursement issues

Categories of Cancer Pain Syndromes

- Neuropathic pain
  - Associated with ChemoTx-induced peripheral neuropathy
  - Paclitaxel associated with grade 3/4 neuropathy in up to 14% of patients with EC
- Post-operative pain
- Myalgias/arthralgias
- Skeletal pain
- Myofascial pain
- GI/urinary/pelvic pain

Management

- Multidisciplinary approach
  - Pharmacologic tx
    - Antidepressants, anticonvulsants, steroids
    - Opiates, NSAIDs, muscle relaxants, patches
  - Psychosocial/behavioral interventions
    - Relaxation training, cognitive-behavioral tx
  - Physical therapy/exercise
  - Interventional procedures
    - Transcutaneous electric nerve stimulation
    - Dorsal column stimulation

Brogan et al.  J Support Oncol 2010;8:52
Reassessment

- Survivors should be reassessed at regular intervals
- Survivors should be re-screened for new late and long-term effects of cancer tx effects
- Outcome assessment
  - Survivor satisfaction
  - Improved adherence to guideline recommendations for health behaviors

NCCN Guidelines Version 1.2013 Survivorship
Survivorship Research

- Paucity of longitudinal cohort studies linking cancer tx with late effects

- Research needed to increase understanding of prevalence, mechanism and risk factors for tx effects

- Research may elucidate optimal follow-up and surveillance schedules
Conclusions

- Most EC recurrences occur in the first 3 years
- Chemotherapy agents used to tx EC include carboplatin, paclitaxel and doxorubicin
- Long-term toxicity includes neuropathy, fatigue and cognitive impairment
- Future research may help better define optimal surveillance schedules for survivors