

**GBMC Head and Neck Conference**

**The Role of Docetaxel in  
the Treatment of Head  
and Neck Cancer**

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December 7, 2007

- Needs assessment:

- Providers who participate in the care of head and neck cancer patients should be aware of the newest evidence for novel chemotherapeutic agents. Recent multi-center randomized-controlled trials provide support for the use of Docetaxel in head and neck cancer.

- Objectives:

- 1) Provide an overview of the mechanism and use of taxane drugs.
- 2) Review recent clinical evidence supporting the use of Docetaxel

- Financial Disclosure:

- None

# Case Presentation

- CC: Worsening dyspnea
- HPI: 63 y/o retired office manager with subacute to acute worsening dyspnea. Evaluation by ENT who identified a transglottic tumor, development of acute SOB required admission to hospital and emergent trach.
  - PET/CT – Mass involving R larynx, extending through cricoid cartilage with involvement of soft tissue anterior, 8 mm jugular node on R; no distant metastases identified
- PMH: COPD, depression, breast cancer, macular degeneration, HTN
- PSH: R mastectomy + neoadjuvant / adjuvant chemotherapy
- SH: 80 pack-year smoking hx, rare ETOH, no other drugs of abuse
- Medications: Paxil, Spiriva, Albuterol, Protonix

# Case Presentation Cont.

## ■ Surgical Treatment:

- 12/06 – Emergent tracheotomy, PEG
- 1/07 – Total laryngectomy, B ND 2A-4, TEP, paratracheal dissection
- Pathology: Negative margins, + perineural invasion.  
4/20 nodes on R, 0/18 nodes on L

## ■ Medical Treatment:

- Recommended chemoradiation but pt declined

# Case Presentation cont.

- 7/07: Presented to head & neck cancer center with small fistula, bleeding
- 8/07: Central neck mass, biopsy proven SCC
  - CT scan: 4x5x4 cm recurrence in hypopharynx, extending to BOT and oropharynx
  - PET: Multiple lung nodules suspicious for malignancy, possible involvement of mandible
- Medical Oncology consult
  - Due to personal hx of chemotherapy, metastatic disease pt recommended for investigational plan utilizing cisplatin, docetaxel, and panitumumab.
    - Panitumumab (Vectibix) – human monoclonal antibody to EGF receptor. FDA approved for EGFR-expressing metastatic colon cancer. IgG2 antibody, cetuximab is an IgG1 antibody.
    - Receiving – Cisplatin, Taxol, 5-FU

# Taxol (paclitaxel)

- 1955: NCI sets up screening for anti-cancer compounds
- 1960: NCI commissions USDA to collect 1000 biologic specimens per year
- 1962: Specimen collected from Pacific Yew tree *Taxus brevifolia*
- 1964: Found to be cytotoxic, purified, published
- 1971: Chemical structure

# Taxol cont.

- 1978: Activity in xenografts, leukemic mice
- 1979: Mechanism of action published in *Nature*
  - Binds to beta subunit of tubulin, hyperstabilizes microtubule structure – causes arrest of ‘dynamic instability’, arrests mitosis, causes apoptosis
- 1982: Animal studies
- 1984: Phase I human studies – 60,000 tons of bark
  - USDA program shut down in 1981 – 114,000 plant; 16,000 animal compounds tested
- 1989: Published data from Phase II trial showed 30% response rate in end stage ovarian cancer

# Taxol cont.

- 1989: NCI announces open Cooperative Research and Development Agreement with drug company willing to commercially develop, synthesize compound, and fund clinical studies
  - Proprietary access to data, all biologic specimens
  - BMS wins contract, files for patent application (granted in 1992)
  - 5 year exclusive marketing rights
  - 2003 Congressional Accounting Report found that NIH “failed to ensure value for money”

# Taxol cont.

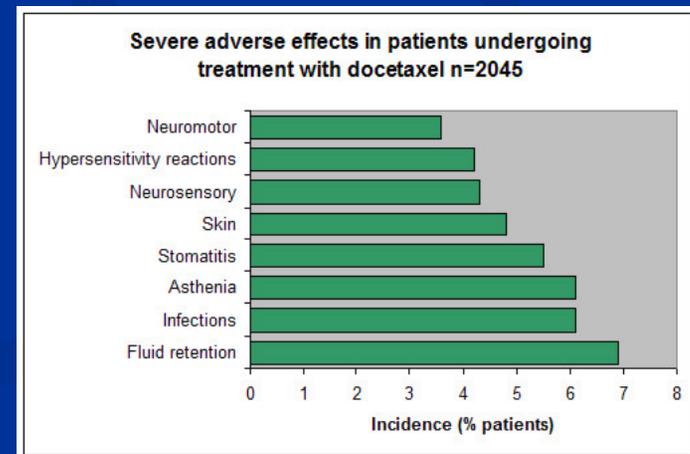
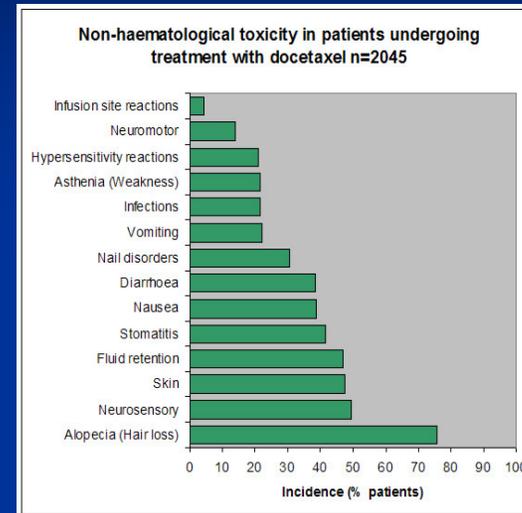
- Until 1993, almost all compound produced was from bark of Pacific Yew
  - 40 ft tree, 200 years old produces 0.5 g of taxol
- Pierre Potier (France): semi-synthetic process using needles of *Taxus baccata* but with poor yield
- Robert Holton (FSU): improved yield to 82% by 1992
  - deal signed between BMS and FSU to patent this and all future synthetic processes
    - Total synthetic synthesis in Dec, 1993
- 1995: BMS announces end of reliance on Pacific yew
- FSU totals over \$200 million in royalties from BMS

# Docetaxel (Taxotere)

- Marketed by Sanofi-Aventis
- Semi-synthetic analogue of Taxol
  - From European yew tree
  - Developed in France following synthetic pathways discovered by Pierre Potier
- Identical mechanism of action, longer microtubule chains
  - Resistance to paclitaxel does not imply resistance to docetaxel

# Docetaxel cont.

- IV formulation – 100% bioavailability
- Liver metabolism
- Hematologic side effects
  - Neutropenia – 95%
  - Anemia – 90%
  - Febrile neutropenia – 11%
  - Thrombocytopenia – 8%
- Death 1.7%
  - Incidence ~10% in patients with elevated liver enzymes



# Chemotherapy Definitions

- *Induction / Neoadjuvant*: Use of chemotherapy before other treatment (surgery or radiotherapy)
- *Concomitant / Concurrent*: Use of chemotherapy simultaneously with other treatment
- *Adjuvant*: Use of chemotherapy in postoperative setting
- *Palliative*: Use of chemotherapy without curative intent

# Chemotherapy and H+N cancer

- 60% of patients present with Stage III/IV disease
- Chemotherapy and radiation the standard of care for majority of locally advanced and unresectable disease
  - *Hyperfractionated irradiation with or without concurrent chemotherapy for locally advanced head and neck cancer.* Brizel DM, N Engl J Med. 1998 Jun 18;338(25):1798-804 [116 pts]
    - Large survival benefit for concurrent therapy compared to radiation alone
  - *Radiotherapy plus Cetuximab for Squamous-Cell Carcinoma of the Head and Neck.* Bonner JA, N Engl J Med 2006 Feb 9; 354(6):567-78. [424 pts]
    - Addition of cetuximab improved locoregional control and mortality

# Brizel

- Radiation: Hyperfractionated irradiation received 125 cGy twice daily, for a total of 7000 cGy
- Chemotherapy
  - 5 treatments of Cisplatin + Fluorouracil during weeks 1-6
  - 2 extra doses after completion of radiation

# Induction Chemotherapy

- What is the evidence for induction?
- Domenge C. Br J Cancer 2000 [318 pts]
  - Neoadjuvant therapy with cisplatin + fluorouracil for 3 cycles followed by local-regional control (surgery or radiation alone) [1986-1992]
    - Neoadjuvant improved survival regardless of method of local control
- Paccagnella. J Natl Cancer Inst 1994 [237 pts]
  - Neoadjuvant therapy with cisplatin + fluorouracil followed by local-regional control
    - For operable patients, the only benefit from neoadjuvant chemotherapy was a significant reduction in the incidence of distant metastases. For inoperable patients, neoadjuvant chemotherapy improved local control, decreased the incidence of distant metastases, and improved the complete remission rate and overall survival.

# Taxanes and H+N Cancer

- 1994: Docetaxel used as single agent chemotherapy in Phase II trial – response rate of 32% (9% complete)
- 1996: Docetaxel used as single agent chemotherapy in Phase II trial – response rate of 42% (10% complete)
- 2000s: Multiple multidrug Phase II feasibility trials

# 1<sup>st</sup> Article

- **Cisplatin, Fluorouracil, and Docetaxel in Unresectable Head and Neck Cancer**
  - EORTC 24971 / TAX 323 Study Group
  - Multi-center study involving 358 patients accrued between 1999 - 2002
  - Study Design:
    - PF or TPF cycles q3week x up to 4 treatments
    - Imaging of tumor cycles 2 and 4
    - Radiation (either conventional or hyperfractionated) within 4-7 weeks after completion of chemo for 7 weeks
    - Neck dissection 'considered for all patients before radiotherapy and 3 months after the completion of radiotherapy'

# Key Findings

- *Table 1:* Patient Demographics
- *Figure 1:* Majority of patients finished chemotherapy (76% TPF, 66% PF)
  - Similar with respect to number of chemo cycles and duration
  - No difference in radiation treatments
- *Figure 2:* 273 patients had disease progression or died
  - TPF resulted in 28% relative reduction in risk of disease progression or death
  - TPF improved overall survival
- *Table 2:* Higher response and complete response rate in TPF group for both chemotherapy alone and after locoregional control
  - Higher rate of surgery in TPF group (40 vs. 20 pts)
- *Table 3:* Adverse Reactions
  - Higher neutropenia, leukopenia in TPF, most other adverse reactions higher in PF

# Discussion

- Median 2.8 months extension in progression-free survival, median overall survival improved by 4.3 months
- Survival shorter than in other Phase 3 trials
- Hyperfractionated radiation not yet accepted as standard at start of trial

## 2<sup>nd</sup> Article

- **Cisplatin and Fluorouracil Alone or with Docetaxel in Head and Neck Cancer**
  - TAX 324
  - Multi-center study involving 539 patients from 1999 to 2003
    - 37 patients excluded because of computer error in randomization
  - Study Design:
    - PF or TPF cycles q3weeks for 3 cycles (slightly higher dose of F in TPF group compared to previous study)
    - Chemoradiation began 3 to 8 weeks after completion of induction, carboplatin + radiation to 70 Gy over 7 weeks
    - Surgery performed 6 to 12 weeks after chemoradiation for all initial N2 and partial response, N3, or residual disease

# Key Findings

- *Table 1:* Patient demographics
  - TPF group had higher T4 after randomization
- *Table 2:* Very high percentage finish initial chemotherapy, dropout during chemoradiation
- *Figure 1:* 234 pts died at study cutoff (47%)
  - TPF resulted in 30% reduction in risk of death
- *Table 3:* TPF associated with trend toward improved survival in all subgroups
  - Median survival 71 vs. 30 months
  - TPF with less locoregional failure; same amount of distant metastases and second primaries
  - Overall response rate after induction and complete response rate not statistically significant
- *Table 4:*
  - Neutropenia, febrile neutropenia, neutropenic infections higher in TPF
  - Despite this, fewer treatment delays in TPF

# Comparison

- Chemo:
- Radiation:
- Patients:
- Ages:
- Stages:
- Extension of Progression-free survival:
- Extension of Overall survival:

# The Big Question

- Does induction chemotherapy plus radiation give equal results to chemoradiation?
- Does induction chemotherapy function as a complement to chemoradiation?
- Only one Phase 3 trial to compare induction chemo, chemoradiotherapy and radiotherapy alone
  - PF induction equivalent to chemoradiation
  - Both superior to radiation alone