

# **CHEMOTHERAPY FOR ADVANCED UROTHELIAL CANCER OF THE BLADDER**

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# Doctor Terms

- Chemotherapy
  - Drugs used to treat cancer
  - Will “attack” cancer no matter where it is located
- Metastatic
  - Spread beyond organ of origin
  - Name of cancer stays the same
- Urothelial (Transitional Cell) cancer
  - Cancer arising from lining of bladder, ureter, or renal pelvis

# More Doctor Terms

- Peri-operative
  - Around the time of surgery
- Adjuvant therapy
  - Therapy administered after surgery to prevent cancer recurrence
- Neo-adjuvant therapy
  - Therapy administered before surgery to prevent cancer recurrence

# Why Does Cancer “Come Back”?

Microscopic cancer cells, not detectable by current technology and outside of the surgical field grow over time to become detectable and cause the patient problems

# Chemotherapy Timing

## Peri-operative setting

- Cannot see disease
  - “Odds” as to whether it is or isn’t present
  - Cannot tell if chemotherapy is working
- More effective?
- Lack of recurrence:
  - chemo worked *OR*
  - cancer was never there

## Metastatic setting

- Can see the disease
  - Dependent on technology
  - Can tell if chemotherapy is working
- Less effective?
  - <10% cure

# Drugs and Regimens Used

- MVAC (methotrexate, vinblastine, Adriamycin, cisplatin)
  - Developed in 1970's
  - Nothing has ever been proven to be better
- Gemcitabine/Cisplatin
  - Similar in efficacy to MVAC
- Substitute carboplatin for cisplatin
  - Cisplatin may be difficult or impossible to administer due to renal problems
  - Carboplatin likely an inferior drug

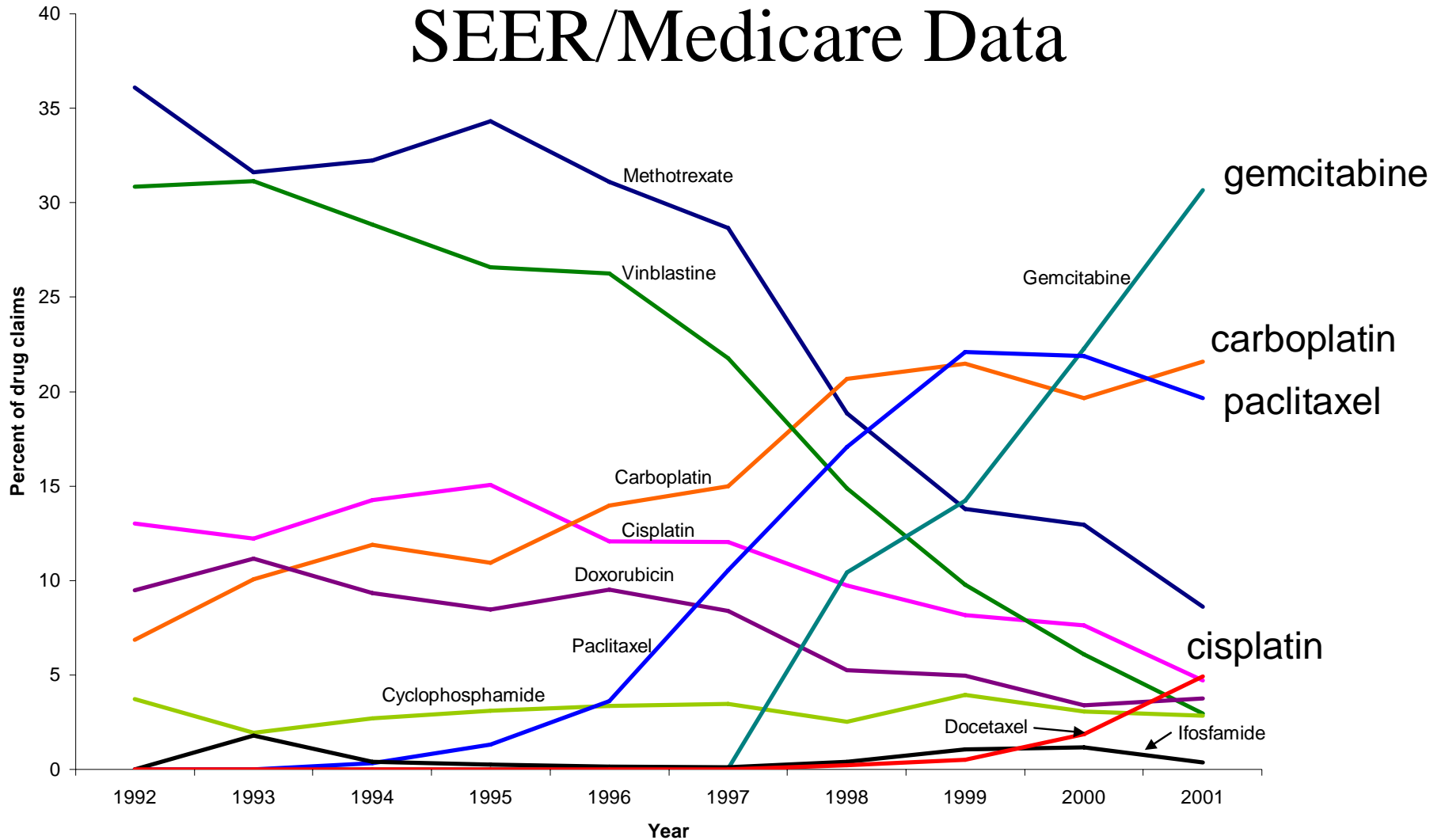
## Comments on “Cisplatin Ineligible”

- Few to no studies with rigorously defined population
- Unwillingness to use up 6 hrs of chair-time to administer necessary fluids: no
- Inability to tolerate fluid load due to CHF: maybe
- Age > xx: no
- Creatinine: no
- Estimated GFR < 30 ml/min: yes
- Estimated GFR 30-50 ml/min: maybe
- Sensori-neuronal hearing loss: maybe
- Peripheral neuropathy > gr 1: maybe

# Other Drugs Being Used

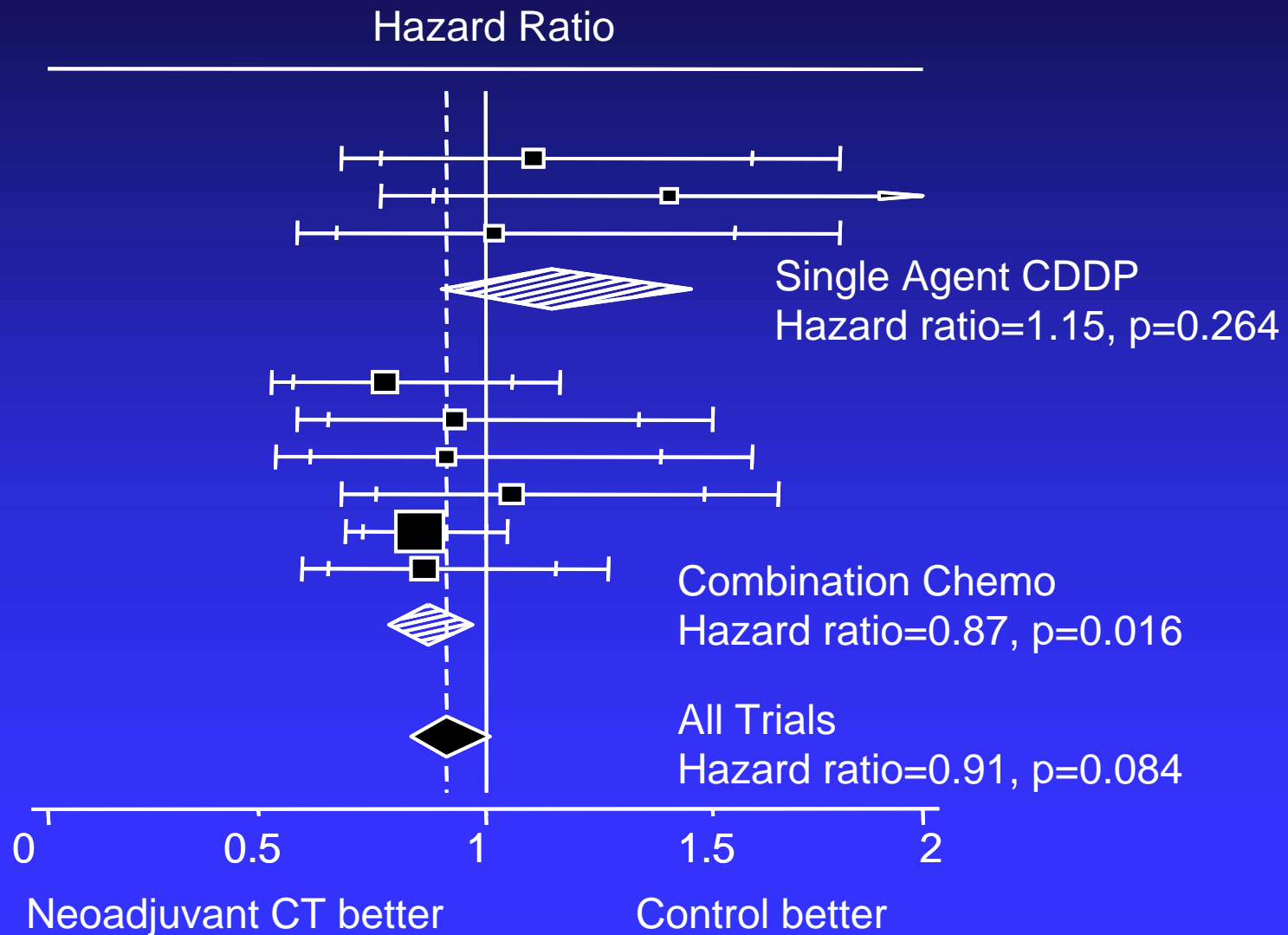
- Paclitaxel (Taxol)
- Docetaxel (Taxotere)
- Vinflunine (investigational)
  - May be approved by FDA for second line therapy
- Ifosfamide

# Chemotherapy Use in Bladder Ca – SEER/Medicare Data



Courtesy, M. Porter; 9/07

# Neoadjuvant Chemotherapy for Bladder Cancer



# What About Adjuvant Therapy

- Since chemotherapy attacks systemic disease, does it matter whether it is given before or after surgery?
  - For efficacy probably no
  - For tolerability maybe
- What is the data
  - Previous studies too small
  - Only available current study of immediate versus delayed chemotherapy is suffering from poor accrual

# Perioperative Chemo in Practice

- National Cancer Data Base
  - 1998 – 2003
  - Estimated 60% of all US cases
  - 11,339 cases of Stage III; 7,161 analyzed
- 11.6% of pts received peri-operative chemo
  - 10.4% adjuvant
  - 1.2% neoadjuvant
  - Increase from 11.3% - 16.8% over time

# What Are We Doing to Improve Chemotherapy?

- Testing vinflunine/gemcitabine first line for patients who cannot tolerate cisplatin
- Adding antiangiogenic bevacizumab first line
  - Phase II gemcitabine/cddp/bevacizumab
  - Phase III gemcitabine/cddp ± bevacizumab
    - Planning stage
- Testing antiangiogenic sunitinib “maintenance” following first line therapy
- Testing antiangiogenic VEGF-Trap 2<sup>nd</sup> line

# Conclusions – Metastatic Bladder Ca

- Metastatic bladder cancer is a chemotherapy sensitive disease
  - Palliation possible in many if not most patients
  - Cure possible, but only in a small minority
- A standard of care remains MVAC
  - Very rare cures in metastatic disease
    - Apparently requires CDDP
  - Optimal therapy for CDDP-ineligible pts is not defined

# Conclusions – Perioperative Therapy Bladder Cancer

- Neoadjuvant therapy is a reasonable standard
  - 2 studies and a meta-analysis with modest survival benefit
  - No selection of patients most likely to benefit
- Adjuvant therapy makes sense, but current data inadequate
  - Opportunity to “target” therapy to patients most likely to benefit
  - current clinical trials should be supported

# Extra Slides

# Neoadjuvant Therapy - “Bladder Preservation”

- Approach
  - Aggressive TURBT (no visible tumor) - *urologists*
  - Neoadjuvant chemotherapy - *oncologists*
  - Combined chemo/RT - *radiation oncologists*
  - Early cystectomy if no complete response - *pathologists*
- Many phase II trials (highly selected patients)
- Approach is feasible with survival rates similar to cystectomy series
- Not a good option for “surgically unfit”

# Bladder Preservation: The MGH Experience

- 190 pts, median f/u 6.7 years
- CR = 63%
  - 37% in pts with hydronephrosis
- 5-yr disease specific survival: 63%
  - T2: 74%
  - T3-4a: 53%
- Cystectomy: 35%
  - 44 with initial incomplete response
  - 25 with subsequent invasive recurrence

# Other RT/Chemo for Bladder Preservation

- 5FU/Leucovorin and RT
- Paclitaxel/Carboplatin and RT
- Paclitaxel/Cisplatin and RT
- Gemcitabine/(Cisplatin) and RT