

## Management of Invasive Systemic Bladder Cancer

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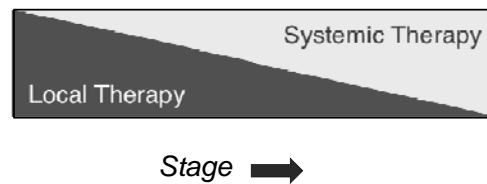
## Disclosures

- **Financial Disclosure:** I have no significant relationships to disclose
- **Off-label Discussion:** Virtually everything in presentation

## Objectives

- Identify clinical features associated with systemic dissemination of clinically localized bladder cancer
- Know expected cure rates for locally advanced bladder cancers in context of current therapy
- Know the natural history of metastatic bladder cancer

## The Big Idea



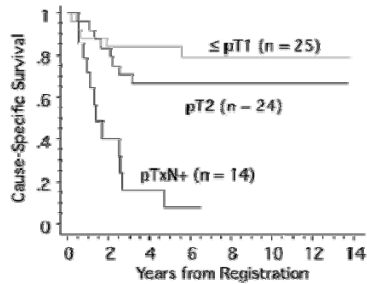
## Which Cancers Require Systemic Therapy?

- Well-Established Indications
  - Hydronephrosis
  - Lymphovascular Invasion on TUR material
  - Involvement of bladder neck
  - Small cell histology
  - Clinically extravesicular disease (cT3b, cT4a)
  - Primary arising in a diverticulum
- Possible Indications
  - Micropapillary histology
  - Sarcomatoid histology
  - Lymphovascular invasion in cystectomy specimen

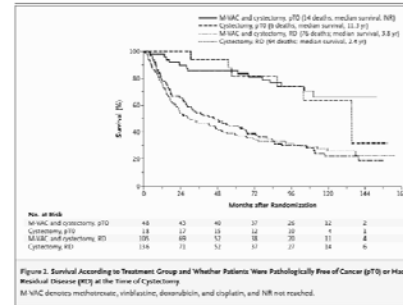
## All T<sub>2</sub> but very different cancers



### Results of Pre-op vs. Post-op M-VAC (MDACC)



### Results of Pre-op vs. Post-op M-VAC (SWOG)



### Perioperative Chemotherapy

- Average risk cT2? **NO**
- High risk cT2, cT3b, cT4a? **YES**
- pT3, pN0? **NO**
- pT<sub>any</sub>, pN1? **YES**
  
- Expectation of Cure is 60 to 70% with combined modality treatment in cN0 patients
  
- In context of neoadjuvant therapy, response in primary is the most powerful prognostic feature

### Front-line Chemotherapy

- M-VAC
- Gemcitabine / Cisplatin
- (Dose-dense versions of above)

### Dose-density

- The only improved results in a direct comparison with classic M-VAC have been from dose-dense MVAC

### Classic M-VAC vs. Dose-dense schedule

- Less mucositis and less neutropenic fever on dose-dense arm
- Results marginally better:
  - CR rate: 21% vs. 9%
  - Survival at 2 years: 25% vs. 12%

### Dose-density

- The only improved results in a direct comparison with classic M-VAC have been from dose-dense MVAC
- For Gem / Cis, the "Lilly schedule" (Gem d1, 8, 15; CDDP d1; q 28 days) is undeliverable
- It is extremely likely that a q 14 version of Gem/Cis is the better way to use this doublet (ASCO *abs* 4510; 2011)

### Front-line Chemotherapy

- M-VAC
- Gem/Cis
- (Dose-dense versions of above)
  
- Gemcitabine / Doxorubicin
- Ifosfamide / Paclitaxel / Cisplatin
- Ifosfamide / Doxorubicin / Gemcitabine

### An Illustrative Case

- 61 y.o. NASA engineer
- Opened and Closed, 2/03. Rind of tumor at peritoneal reflection, bilateral UVJ obstruction, biopsy proven omental involvement, creatinine > 2
- Chemo, Chemo and more Chemo

### Chemotherapy!

- 5/03 - 8/03      Gem, Paclitaxel, Doxorubicin
- 8/03 - 10/03     Gem, Doxorubicin, Cisplatin
- 10/03 - 11/03    Dose-dense MVAC
- 11/03 - 1/04     Ifosfamide, Doxorubicin, Gem

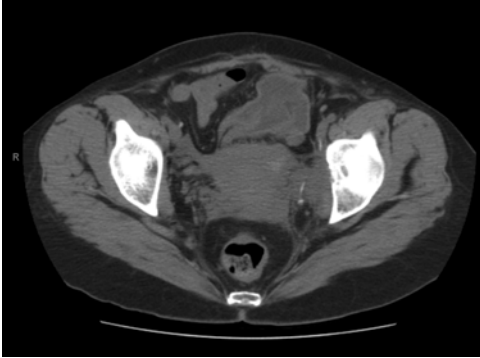
### An Illustrative Case

- 61 y.o. NASA engineer
- Opened and Closed, 2/03. Rind of tumor at peritoneal reflection, bilateral UVJ obstruction, biopsy proven omental involvement, creatinine > 2
- Chemo, Chemo and more Chemo
- No residual invasive cancer at cystectomy 3/04; NED for 16 months, then explosion

### Case 2: The Limits of "Locally Advanced" ?

- 53 year old woman presented with pelvic recurrence 14 months after pT2, No (0/18) resection
- Barely able to walk secondary to invasion of acetabulum

Pelvic recurrence with invasion of bone.



#### Clinical Course

- Dose-dense MVAC x 3 with minimal shrinkage
- Ifosfamide based regimen x 3 with resolution of pain, CR by CT, and remineralization of bone
- XRT to acetabulum
- Surgery 7 mo after chemotherapy (EBL 2.4 L)
- No residual malignancy in surgical specimen
- NED now >3 yrs out

#### Front-line Chemotherapy

- Response rates are high
- Toxicity and expense are high
- Cure of grossly metastatic disease is still RARE
- Survival is NOT tightly coupled to response rate
- The cytotoxic paradigm probably isn't going to get us where we need to be

Insanity: *Doing the same thing over and over again and expecting different results. (Einstein)*



#### Where will we find a better way?

- Better identification of at risk patients

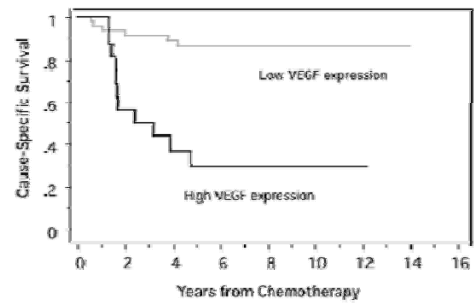
#### Patient Identification

- Gain of 1q23.3 recently shown to stratify outcome among patients getting platinum-based therapy (ASCO *abs* 4569; 2011)
- What is more urgently needed are markers predicting benefit from available therapy

Where will we find a better way?

- Better identification of at risk patients
- VEGF-R related agents showing some promise

Cause-Specific Survival by VEGF expression



Pazopanib for Urothelial Cancer

- First reported at ESMO, 2010
- Updated recently (ASCO *abs* 4618; 2011)
- Reported 13% RECIST PR, and 67% Stable Disease among chemotherapy failures; 16/30 patients had liver mets

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- Immune approaches are of interest

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- Better identification of at risk patients
- VEGF-R related agents showing some promise
- Immune approaches are of interest
  
- Bladder cancer usually presents before overt metastatic disease, and should be amenable to significantly improved cure rates with optimal integration of available therapies