Chemotherapy for Urological Cancers

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Chemotherapy for Urologic Cancers

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- Q: What is Chemotherapy?
- A: In *oncologic* terms, chemotherapeutic agents are chemicals with varying mechanisms of action that influence cell survival by damaging DNA. May be:
  - Cytotoxic
  - Cytostatic

Chemotherapy Schemes

- Adjuvant/neoadjuvant
- Palliative
- Survival benefit
- Curative

- Various roles in:
  - RCC
  - Bladder cancer
  - Testicular cancer
  - Prostate cancer

Chemotherapy Principles

- Very narrow therapeutic index.
- We do not understand why cancer cells are preferentially responsive to chemotherapeutic agents. In fact, the abundance of data suggest that for the vast majority of human malignancies, the converse is true. That is, certain normal cellular compartments are *more* sensitive to the effects of chemotherapy than cancer cells.

RCC

- Chemotherapy has no role.

Bladder Cancer

- Neoadjuvant (pre-op): combination chemotherapy improves OS.
  - ~5% improvement at 5 years.
  - Applies to all stages.
- Data in adjuvant (post-op) setting is controversial and less robust.
- Chemotherapy (cisplatin) plus radiation is a bladder-sparing option for tumors optimally debulked by TURBT with no clear decrement in OS.
  - Bladder spared in ~50% of cases.
  - Prognostic factors: performance status, visceral involvement, p53 mutations, ERCC1 mutations.

Bladder Cancer

- Metastatic: Combination chemo improves OS.
  - ~12 mos vs. 6 mos for BSC.
  - Gemcitabine and cisplatin (GC) is "non-inferior" to MVAC, but less toxic.

Testicular Cancer

- Adjuvant chemotherapy for stage I and II markedly reduces recurrence risk, but does not affect overall survival because salvage therapy of patients managed by observation is effective.
- Metastatic disease: chemo is curative.
  - Good risk: 90% cure.
  - Intermediate risk: 70% cure.
  - Poor risk: 50% cure.

Testicular germ cell tumors risk stratification system
Seminomas
Good risk
All of the following:
Any primary site
No nonpulmonary visceral metastases
Normal serum AFP
Intermediate risk
All of the following:
Any primary site
Nonpulmonary visceral metastases present
Normal serum AFP

Non-seminomatous germ cell tumors
Good risk
All of the following:
Testicular or retroperitoneal primary tumors
No nonpulmonary visceral metastases
Serum AFP <1000 ng/mL, beta-hCG <5000 mIU/mL, and LDH <1.5 times upper limit of normal
Intermediate risk
All of the following:
Testicular or retroperitoneal primary tumors
No nonpulmonary visceral metastases
Intermediate level of any of the following:
AFP 1000 to 10,000 ng/mL
beta-hCG 5000 to 50,000 mIU/mL, or
LDH 1.5 to 10 times upper limit of normal
Poor risk
Any of the following:
Mediastinal primary, or
Nonpulmonary visceral metastases, or
Serum AFP >10,000 ng/mL, or
Serum beta-hCG >50,000 mIU/mL, or
LDH more than 10 times upper limit of normal

Prostate Cancer

- No established role for chemotherapy in the neoadjuvant/adjuvant setting.
- Metastatic disease:
  - Docetaxel improves OS
    - Median OS improved 2-3 mos.
    - Reduces risk of death by ~ 25%.
  - Mitoxantrone
    - No affect on survival.
    - Improves QOL of patients with bone pain.

Case 1

Date	Case History	PSA
2/2006	• 55 yo AAM undergoes open RRP: Gleason 5+4 = 9/10, SVI (pT3b), PNI, SM-.	8.5
5/2006		1.2
7/2006	• LHRH analog initiated.	3.8
9/2006		0.8
12/2006	• Patient c/o bone pain, fatigue. • Bone scan: widespread bone mets. • CT abd/pelvis: RPLAN and liver mets. • CRPC diagnosed based on clinical and radiographic progression.	0.8

What is the next step?

Case 1

Date	Case History	PSA
1/2007	• Liver biopsy → neuroendocrine (small cell) carcinoma. • Chemotherapy initiated (cisplatin/etoposide).	
3/2007	• Restaging CT abd/pelvis → partial response. • Chemotherapy continued for a total of four cycles.	
11/2007	• Restaging CT abd/pelvis → progression of liver mets. • Patient's performance status rapidly declines. • Referred for hospice care.	

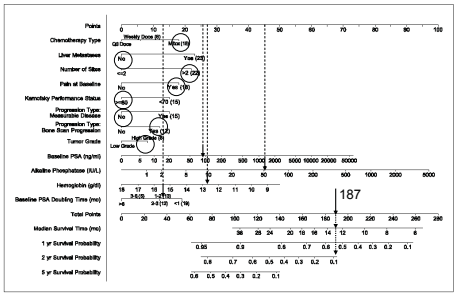
Case 2

Date	Case History	PSA
1991	• 62 yo WM. RRP: Gleason 4+4 = 8/10, pT2b.	6.2
1991-97		undetectable
1998	• Lupron/Casodex initiated.	3.7
1998-2007		undetectable
1/2007	• T = 4.0 ng/ml; CRPC diagnosed.	1.2
3/2007	• Casodex withdrawn.	4.8
5/2007	• Bone scan → widespread mets associated pain. CT abd/pelvis - • CRPC with clinical, radiographic and PSA progression. • Ketoconazole/hydrocortisone initiated.	11.8

Case 2

Date	Case History	PSA
6/2007	• LFTs elevated → ketoconazole/hc d/c'd.	38.4
7/2007	• LFTs normalize.	85.2

CRPC Nomogram



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Case 2 (continued)

Date	Case History	PSA
8/2007	• Chemotherapy (docetaxel) initiated.	95.1
9/2007	• Bone pain resolved. • No significant chemotherapy-related toxicity.	31.5
10/2007		8.6
11/2007		4.6
12/2007		1.6
1/2008	• Bone scan: no evidence of progression.	0.8
5/2008	• Chemotherapy completed (10 of 10 planned cycles).	0.5

Survival by PSA Decline from TAX 327

	Median Survival (months)
PSA normalization (n=115)	33.3
≥ 90% PSA decline (n=106)	26.6
≥ 50% PSA decline (n=460)	22.4
≥ 30% PSA decline (n=591)	21.6
Any PSA decline (n=730)	20.7
No PSA decline (n=259)	11.7

Armstrong, AJ et al. *J Clin Oncol* 2007; 25 (18S Part I of II):237S (abstract and oral presentation 5009).

Case 2

Date	Case History	PSA
?	Progression	↑↑

No established therapy for docetaxel-resistant CRPC.

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Clinical trials.