Continued on separate pages:

1. Future directions in bladder cancer research- Genetic Markers;
   Gigliola Sica -Chairman Institute of Histology and Embryology,
   Faculty of Medicine Catholic University of the Sacred Heart Rome

2. Newer non-invasive diagnostic tools in bladder cancer
   M J Bailey, St. George’s Hospital, London

3. ISUP-WHO tumor classification: really the gold standard?
   Fabio M. Vecchio Ist. Anatomia Patologica, Università Cattolica Roma

4. Markers of recurrence and progression Prof. Fred Witjes Radboud UMC Nijmegen, the Netherlands; Innovations in Urology: Bladder cancer Rome; December 2, 2005

Separate pages:

8. The effect of heat dose on clinical outcome A.G. van der Heijden; University Medical Centre Nijmegen The Netherlands

9. Local hyperthermia and intravesical chemotherapy for superficial TCC of the bladder Clinical studies: An overview; R. Colombo U.O. di Urologia Istituto Scientifico Universitario “Vita e Salute”; San Raffaele, Milano

10. Thermo-chemotherapy: Preliminary results of current international studies Prof. Fred Witjes Radboud UMC Nijmegen, the Netherlands Innovations in Urology: Bladder cancer Rome, December 2, 2005

11. Thermochemotherapy - Current Italian Studies Rodolfo Hurle U.O. Urologia Humanitas Gavazzeni Bergamo
Reliable data

The impact of intravesical chemotherapy on tumor recurrence and progression is still an open question. In 2000 [Huncharek M., 2000], a meta-analysis was done using 1672 citations which compared Turb vs Turb + chemo

Primary vs Recurrent

? 1-yr follow-up

Endpoint: Recurrence

It was determined that only 11 out of the 1672 studies fit the criteria of a randomized, controlled clinical trial. A total of 3701 patient histories were examined using recurrence as an end point. It was determined that of the drugs: Thiotepa, Epirubicin, Mitomycin C and Mitoxantrone - Mitomycin C was the most effective. A single instillation can delay recurrence at 1 year by 30%, multiple instillations by 31% after 2 years.

Chemo vs BCG

In another meta-analysis, from 97 citations, 9 fit the required criteria [Huncharek M., 2003]: Randomized controlled clinical trials comparing intravesical chemotherapy to BCG, with a minimum of 2 years follow up and more than 20 patients per arm. A total of 2261 cases were examined; the conclusions were:

--There is little advantage of BCG over intravesical chemotherapy, about 11%

--The currently perceived superiority of BCG may be an artifact since most randomized trials include chemotherapy
failures.

--47% of people who fail intravesical chemotherapy respond to BCG as second line treatment.

Chemo vs BCG on progression

Another meta-analysis [Huncharek M., 2004] failed to support a clear superiority of BCG over intravesical chemo regarding tumor progression. Mitomycin C was the more effective chemotherapy drug. Having failed intravesical chemotherapy causes a spurious finding of greater BCG effect.

Chemo vs BCG on Carcinoma in situ

A meta-analysis of randomized controlled trials with the inclusion criteria of primary, secondary or concurrent CIS was performed [Silvester R., 2005]. From a total of 14 citations, 9 fit the criteria and 700 cases were examined. It was concluded that BCG had a superior effect on disease-free status, but no clear conclusions can yet be drawn regarding the impact of BCG on long term survival.

Problems with published data

The number of trials that fit criteria must be standardized
The number of patients included is not high enough to draw concrete conclusions
The follow-up lengths vary
There are different treatment protocols used
No distinction is made between primary, secondary or recurrent CIS

While meta-analysis does support important information, more questions remain to be answered via properly designed and adequately powered randomized trials

Is there a solution?

Critical evaluation must lead to innovation and standardization regarding terminology, treatment strategies and methodology/end points.

What we can say about superficial bladder cancer is that it's a peculiar disease known for:

- high incidence of recurrences
- negligible incidence of progression (>T2)
- relevant role of endoscopic treatment/management and intravesical therapy
- the limited role of imaging tools
The main questions that remain open are:

--who is the optimal candidate
--what's the best drug? How does it work?
--what's the optimal regimen- best time for beginning treatment?
--how long should the drug be kept in the bladder?
--what is the ideal interval between instillations?
--what dose should be given at each instillation?
--how long should the drug be administered? Maintenance, no maintenance?
--in what liquid and what volume should it be dissolved?
--will all tumor respond to the treatment?
--what's the influence of diuresis, urinary pH, concentration, etc?
--what's the overall cost/benefit ratio?

Factors altering the citotoxicity

--molecular weight
--lipophilicity
--pH
--osmolarity - concentration
--dosing volume
--dose

There is in fact little data to answer the above questions. The European guidelines currently support the approach of one intravesical chemotherapy instillation immediately following TUR [see:EORTC meta-analysis-Perspectives in bladder cancer on webcafe]

Principles of intravesical therapy: Possible benefits

--high drug concentration is possible
--direct contact is made between tumor and drug
--prolonged contact time
--decreased systemic side effects

The ideal drug should be
--active in eradicating the pre-existing disease and in preventing both recurrence and progression
--the simplest and shortest administration
--no side effects
--reasonable cost

The pivotal assessment of prognostic factors and risk categories must first be obtained:
patient's history of disease
voided cytology
imaging -IVP, Ultrasound
Cystoendoscopy
--Transurethral Resection of Bladder Tumor(s) TURBT
--Bladder mucosa cold biopies
-- Bimanual Palpation under Anesthesia
Check cytology/endoscopy

Dose vs activity vs toxicity
There is uncertainty regarding the best dose-activity ratio for intravesical chemo/immunotherapy; Generally the higher the dose, the higher the toxicity for both chemo and immunotherapeutic agents

Dose vs activity-
Epirubicin for Carcinoma in situ KURTH, J. UROL 199

Dose
% complete reponse

30mg
43

50mg
60

60 mg
70
Multi-centered, EORTC randomized controlled clinical trials:

Single and early instillations:


Early vs. Delayed instillations


Optimal time between instillations- very little data.

One randomized study [Burk, Urologe 1986] compared 3 similar groups:

Group 2: weekly instillatoins for 1 month
Group 2: 2-week interval instill. for 6 months
Group 3: monthly instill. for 1 year
Surprisingly no difference in outcomes were found.

The usefulness of added courses of chemotherapy after treatment failure

40 patients with carcinoma in situ were treated with either Adriamycin or Mitomycin [Solsona, Eur. Urol. 1991]:

Response-52%
Non response-48%

Of the non-responders, 12 of them went on to a second course, of these patients the rate of response was:

Response-57%
No response-43%

Additional course of 6 wks BCG
Publication
No pts
+response
median follow up (mos.)

Catalona, JUrology '87
49
20%
15.8

Kavaoussi, JUrology '86
57
60%
17.5

Bassi, JUrology '92
44
50%
21

BCG maintenance vs. No Maintenance

A SWOG (Southwest Oncology Group) study [Lamm, 2001, JUrology] presented data showing improved disease free status, favoring additional BCG maintenance for carcinoma in situ and Ta, T1 tumors:

+Maintenance: 83% vs 65% no maintenance

+Maintenance: Ta - T1: 83% vs 50% -no maintenance

Polichemotherapy

There is some 'in vitro' evidence [Seraphim JUrol.1991] that intravesical chemo agents work synergistically:

Doxorubicin + Thiotepa

Doxorubicin + Mitomycin C

This approach was tested in vivo [Ferraris, Cancer 1988]

60 Pts, stage Ta - T1, treated with TUR followed by doxorubicin, 50 mg /30 ml + Mitomycin C, 20 mg/20 ml, for 6 weeks + 10 months maintenance, for a response rate of 70% at mean follow up 28 months.

Question: What is the optimal timing?

Chemo followed by immunotherapy?

Immunotherapy followed by chemotherapy
Chemo followed by chemotherapy?

Immunotherapy followed by immunotherapy?

Second line chemo after chemo-some results

<table>
<thead>
<tr>
<th>agent</th>
<th>#pts.</th>
<th>treatment</th>
<th>%response</th>
<th>author</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMC after TIPA</td>
<td>23</td>
<td>Proph/Ter</td>
<td>43%</td>
<td>Prout, J.Urol, '82</td>
</tr>
<tr>
<td>MMC after TIPA</td>
<td>57</td>
<td>Proph/Ter</td>
<td>42%</td>
<td>Issel, Cancer, '84</td>
</tr>
<tr>
<td>TIPA after MMC</td>
<td>5</td>
<td>Prophylactic</td>
<td>60%</td>
<td>Zincke, J.Urol '85</td>
</tr>
<tr>
<td>MMC after ADM</td>
<td>31</td>
<td>Prophylactic</td>
<td>42%</td>
<td>Bassi, Urol.Int. '92</td>
</tr>
</tbody>
</table>

Second line chemo after BCG:
%response
author

MMC
4
prophylactic
100%
Pinon, J.Urol, '88

MMC
11
Proph/Ter
82%
Rintala, Eru.Urol, '91

'Rescue' BCG therapy for relapse after successful BCG treatments:
Response -78%
Non response -22% (PROG. 5%)[Bassi J.Urol 1993]

Investigative agents:
Oral megadose vitamin - Lamm, J. Urol. 1994

Conclusions, What we do know with certainty:

No ideal drug exists yet
Optimal conditions for I.V. administration established but not applied
Value of:
Single instillations
Early course
Maintenance Therapy
Additional course
Second line therapy
Intravesical therapy is not strictly necessary

"THE ILLUSION OF KNOWLEDGE IS THE MAJOR OBSTACLE TO THE PROGRESS" Prof. Bassi
6. Innovative Treatments - Newer Chemotherapeutic Drugs; C Barone, Oncologia Medica, Università Cattolica S. Cuore, Roma. 2005

This presentation covers new agents being tried for superficial and advanced bladder cancer.

Systemic chemotherapy is reserved for higher stage disease as:

Neoadjuvant Therapy
Adjuvant Therapy
Palliative Therapy (Metastatic Disease)

New drugs for advanced (metastatic) disease:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Response Rate % - phase II trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine</td>
<td>28</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>42</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>31</td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>26</td>
</tr>
<tr>
<td>Epothilones</td>
<td>n.e.</td>
</tr>
<tr>
<td>Vinflunine</td>
<td>n.e.</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>n.e.</td>
</tr>
</tbody>
</table>

http://blcwebcafe.org

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Generated: 27 August, 2017, 07:41
Gemcitabine: Deoxycitidine analogue, pyrimidine antimetabolite, that interferes with DNA synthesis via a direct inhibition of ribonucleotide reductase or by means of incorporation of difluorodeoxycytine monophosphate into DNA. As final results GMC inhibits cell growth and trigger apoptosis.

Pemetrexed: Folate analogue, that enter the cell through the reduced folate carrier; undergoes polyglutamation and is retained into the cell

Epithilones: Semisynthetic analogues of the natural Epothilones A and B, which have a mode of action similar to taxanes (microtubules stabilization)

Active in both paclitaxel sensitive and refractory tumours; Twice as potent as Paclitaxel in-vitro

Vinfumine: A novel fluorinated Vinca alkaloid

Advanced/Metastatic Bladder Cancer - Molecular Targets

<table>
<thead>
<tr>
<th>Target</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFGR</td>
<td>Overexpressed in 31-48% BLC; Associated with poorer outcome and higher stage</td>
</tr>
<tr>
<td>HER2/Neu</td>
<td>Overexpressed in 40% BLC</td>
</tr>
<tr>
<td>Bcl-2</td>
<td>Overexpressed in BLC</td>
</tr>
<tr>
<td>Ras</td>
<td>Mutated in 1-80% BC</td>
</tr>
<tr>
<td></td>
<td>Activating mutation in 10% BC</td>
</tr>
</tbody>
</table>

Inhibitors of EGFR/HER Family

Mabs: Trastuzumab, Cetuximab, Panitumumab

TKIs: Gefitinib, Erlotinib, Lapatinib, ZD6474, etc.
Author
Drug
Mechanism of Action
Results

Petrylak D, ASCO '03
Gefitinib
ErbB1 TKI
RR 3%

Machiels JP, ASCO '04
GW572016
ErbB1/ErbB2 TKI
10%

Wulfing L, ASCO '05
Lapatinib
ErbB1/ErbB2 TKI
RP 3%, SD 20%

Rosenberg JE, Cance, '05
Tipifarnib
Farnesyl transferase inhibitor
RP 18% (naive)
SD 56% (pretr.)

*RR-Response rate; RP-partial response; SD-stable disease

Incorporation of New Cytotoxic Drugs in Clinical Practice

Gemcitabine — 1) GMC+CDDP [Gemcitabine+cisplatin] vs M-VAC : the rationale is that the newer combination of GC gives result very similar to the gold standard, M-VAC but with much less toxicity

GC
M-VAC

Pts.
203
202

Complete reponse%
<table>
<thead>
<tr>
<th>Author</th>
<th>Treatment</th>
<th>Pt's (n.)</th>
<th>RR%</th>
<th>RR%</th>
<th>MS (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carles J</td>
<td>GMC+CBDCA</td>
<td>17</td>
<td></td>
<td>56 (CR 12%)</td>
<td></td>
</tr>
<tr>
<td>Lippert CM</td>
<td>GMC+CDDP or CBDCA</td>
<td>19</td>
<td></td>
<td>45 (CR18%)</td>
<td></td>
</tr>
<tr>
<td>Hussain SA</td>
<td>GMC+fractioned CDDP</td>
<td>32</td>
<td></td>
<td>65.5 (CR12%)</td>
<td>16</td>
</tr>
</tbody>
</table>
3) Doublets without Platinum: The taxanes are also being tried:

<table>
<thead>
<tr>
<th>author</th>
<th>treatment</th>
<th>Pts.(n.)</th>
<th>RR(%)</th>
<th>MS (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sternberg C</td>
<td>GMC+TXL</td>
<td>40</td>
<td>60 (CR 33%)</td>
<td>14.4</td>
</tr>
<tr>
<td>Meluch AA</td>
<td>GMC+TXL</td>
<td>54</td>
<td>54 (CR 7%)</td>
<td>14.4</td>
</tr>
<tr>
<td>Boyer MJ</td>
<td>GMC+TXT</td>
<td>31</td>
<td>50 (CR 10%)</td>
<td></td>
</tr>
<tr>
<td>Srinivas S</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
GMC+TLX
17
65 (CR 17%)
7.5

Ardavanis A
BJC 2004
GMC+TXT
31
52 (CR 13%)
15

 autres doublets sans Platin:

<table>
<thead>
<tr>
<th>author</th>
<th>treatment</th>
<th>Pts. (n.)</th>
<th>RR(%)</th>
<th>MS (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krege S</td>
<td>J Urol 2001</td>
<td>22 (pre-treated)</td>
<td>18</td>
<td>-</td>
</tr>
<tr>
<td>Garcia d Moro</td>
<td>BJC 2002</td>
<td>38</td>
<td>58 (CR 18%)</td>
<td>10.4</td>
</tr>
<tr>
<td>Chaudhary VB</td>
<td>ASCO 2005</td>
<td>10</td>
<td>80 (CR 20%)</td>
<td>-</td>
</tr>
</tbody>
</table>

Triplets with CDDP: Due to the increased toxicity with three drugs, carboplatin may be preferred to cisplatin:
<table>
<thead>
<tr>
<th>Author</th>
<th>Treatment</th>
<th>Pts. (n.)</th>
<th>RR (%)</th>
<th>MS (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bellmunt J</td>
<td>JCO 2000 GMC+TXL+CDDP</td>
<td>58</td>
<td>78 (CR 28%)</td>
<td>15.8</td>
</tr>
<tr>
<td>Maluf F</td>
<td>ASCO 2000 GMC+DOX?IFX+TXL+CDDP</td>
<td>21</td>
<td>86 (CR 43%)</td>
<td>-</td>
</tr>
<tr>
<td>Bajorin D</td>
<td>Cancer 2000 IFX+TXL+CDDP</td>
<td>45</td>
<td>68 (CR 23%)</td>
<td>20</td>
</tr>
<tr>
<td>Clark PE</td>
<td>ASCO 2004 GMC+TXL+CDDP</td>
<td>29</td>
<td>52 (CR 28%)</td>
<td>10.7</td>
</tr>
</tbody>
</table>

**Triplets without CDDP**

<table>
<thead>
<tr>
<th>Author</th>
<th>Treatment</th>
<th>Pts. (n.)</th>
<th>RR (%)</th>
<th>MS (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lara PN</td>
<td>Cancer 2004 GMC+TXL+MTX</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Combination of Targeted Drugs with Cytotoxic Drugs

<table>
<thead>
<tr>
<th>author</th>
<th>treatment</th>
<th>Pts.</th>
<th>comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hussain M</td>
<td>HER+GMC+CBDCA+TXL</td>
<td>44</td>
<td>RR 72.7% CR 11%</td>
</tr>
<tr>
<td></td>
<td>HER2 overexpressing 54%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gene amplification 13%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Philips G</td>
<td>GEF+CDDP+GMC</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>
Other Biological Agents in Pre-clinical Models

agent               comment

Endostatin
Inhibitor of angiogenesis
Inhibits bladder cancer growth

TPN-470
Inhibitor of VEGF derived from Asperg. fumigatus
Inhibits the development of limphonodal metastases

Bortezomib
Proteosome inhibitor
Inhibits bladder cancer growth

Antisense OG
directed at bcl2
Reverses CDDP resistance

Antisense OG
at clusterin
Confers a more chemosensitive phenotype

Combination of Biological Agents and Cytotoxic Drugs in Preclinical Models

agent               comment

CET + TXL
Synergism

IFNa2a+retinoic acid
Synergism; IFN induces retinoic acid receptor β Retinoids increase IFN-related gene expression
TNP-470+GMC
Inhibit tumour growth and metastases

Superficial Bladder Cancer (SBC)- New Drugs

agent
pharmacology

Gemcitabine
Deoxycytidine analogue

Valrubicin
Semisynthetic derivative of doxorubicin

Suramin
Polysulfonated naphtyl-urea

Tipifarnib
Farnesyl-transferase inhibitor

Difluoromethylornithine
False metabolite of ornithine decarboxylase

Fenretinide
Retinoid

Celecoxib
Specific cicloxygenase inhibitor

γ-linoleic acid
Essential fatty acid

Mistletoe extracts
Lectins

Gemcitabine: Characteristics for intravesical use

- Significant activity against invasive BLC
- Molecular weight (299 D) sufficiently low for penetrating bladder mucosa, but high enough to prevent systemic absorption
- Favourable pharmacokinetics and negligible ionisation
Various phase I research has led to the conclusion that Gemcitabine should be used at dose: 2000 mg/sqm/wk (40 mg/ml in 50 ml); Dalbagni G, JCO 2002; Laufer M, JCO 2003; Witjes JA, Eur Urol 2004; Palou J, J Urol 2004.

GMC has antitumor activity comparable to BCG: Intravesical Gemcitabine

Intermediate risk Ta-T1, G1-G2 SBC

<table>
<thead>
<tr>
<th>author</th>
<th>(mg/ml)</th>
<th>q</th>
<th>Pts.</th>
<th>marker lesion</th>
<th>CR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van der Mejden APM</td>
<td>40</td>
<td>wkly x 6</td>
<td>39</td>
<td>1</td>
<td>56</td>
</tr>
<tr>
<td>De Berardinis E</td>
<td>40</td>
<td>wkly x 6</td>
<td>24</td>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td>Serretta V</td>
<td>10-110</td>
<td>wkly x 6</td>
<td>27</td>
<td>&gt;1</td>
<td>22</td>
</tr>
<tr>
<td>Dalbagni G</td>
<td>20</td>
<td>Biwkly x 6</td>
<td>28*</td>
<td>-</td>
<td>57</td>
</tr>
</tbody>
</table>
*BCG refractory high risk

Intravesical Gemcitabine Adjuvant Therapy after TURB:

author
GMC

(mg/ml)
q
Pts
results

Bouzid K
ASCO 2004
20
Wkly x 6
29
0 relapse after 12 m follow-up (3-15)

Gunelli R
ASCO 2005
40
Biwkly x 6
32
3 relapse after 14 m follow-up

Valrubcin-characteristics
Systemic absorption significantly limited, local toxicity, but no progressive bladder contraction; it seems to be less effective than Gemcitabine:

author
VRB

(mg/sqm)
Pts.(n.)
Stage
Results
Greenberg RE
Urology 1997
200-900/w
(MTD 800)
32
Ta/T1
CR 40.6%

Steinberg G
J Urol 2000

800/w
90
Tis
Cr 21% TTF>18 m

Newling DW
Eur Urol 2001
800/w
40
BCG-ref.
CR 46% TTF 8 m

Suramin: Characteristics for intravesical use

- Inhibits proliferation and DNA synthesis
- Is a potent VEGF antagonist
- Blocks the binding of EGF to its receptor
- Large molecular size and negative charge inhibit bladder absorption

Intravesical Suramin, phase I studies:

author
VSRM

(mg/sqm)
Pts. (n.)
Stage
Results

Uchio EM
J Urol 2003
0.6-614/w
Refractory Spasm
Reflux

Ord JJ
BJC 2005
10-150/w 12
12 Recurrent
No tox

Minimal abs at =150
Urinary VEGF reduced

Preliminary Results with other Agents - 1

Tipifarnib
A phase II study is ongoing

y-linoleic acid
>90% growth inhibition in BC lines
4/30 (13%) CR in a phase II trial
(Harris NM, Eur Urol 2002)

DFMO
Suppresses the development of invasive BC in murine models
Preventive effect
Randomized phase III trial in low grade SBC ongoing

Preliminary Results with other Agents - 2
agent
results

Fenretinide
Preventive effect in murine models
One preventive study showed no difference in molecular endpoints and RFS

Celecoxib
Reduces the development of chemically induced BC in mice

Lectins extracted from mistletoe
Enhance NK toxicity
Stimulate cytokine secretion
Induce cytotoxicity and apoptosis in-vitro and in murine models
In a phase II study recurrence rate (33%) in 30 G1-G2 pts comparable to historical BCG
(Elsässer-Behe U, J Urol 2005)

Conclusions 1.:
_GMC and TXNs are highly active in metastatic BC
_Doublets or triplets including GMC and/or TXNs are promising, but have to be compared with standard treatment (GC or M-VAC) in large phase III studies
_Other newer drugs (PEM, Vinflunine, etc) also seem active.

Conclusions 2.:
_Targeted drugs are marginally active, but the preliminary studies have not been adequately designed
_They need to be evaluated in combination with cytotoxic drugs in patients at least expressing the specific molecular target
_GMC efficacy in SBC is comparable to that of BCG
_Other drugs are in early phase of study in SBC, including differentiating agents and some targeted drugs.