WebCafé report by Wendy Sheridan

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November, 2003

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Chair:P.G.Harper, MD, Guy’s Hospital, London, United Kingdom

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D. Raghavan, MD, PhD, University of Southern California Norris Comprehensive Cancer Center Los Angeles, California, USA

Chemotherapy for intermediate risk and BCG for high risk E.Solsona, MD, Valencia Institute of Oncology, Spain

A review of the literature evaluating controlled trials recently showed that intravesical chemo and BCG are both effective at lowering recurrence rates, with either treatment significantly better than TUR alone. However, only BCG+ maintenance was shown to have an impact in reducing progression.1 The question is whether or not BCG remains superior throughout the three classic ‘risk groups’ of low, intermediate and high.

In a review of six randomized series looking at intermediate risk patients, only one BCG trial showed superiority over chemo in decreasing recurrence, with the remaining series showing no significant difference between the two treatments;

Low risk:

recurrence-29-48%, mean of 36.5%; progression-0-7.1%, mean of 3.3%

Inter.risk:

recurrence-45-67%, mean of 57.2%; progression-1.8-17.4%, mean of 9.4%

High risk:

recurrence-54-82%, mean of 73.5%; progression-15-47.35%, mean of 31.5%

The data suggest that the objectives of each group should differ. In the intermediate group the first priority is to reduce the high recurrence rate and secondly to decrease progression rate, while the high risk group’s main objective should be to decrease progression.

There is compelling evidence that early instillation of chemotherapy after TUR reduces recurrence rate in intermediate risk groups compared with late instillation (after 24 hrs). There is not enough evidence to claim that BCG is superior to MMC in the intermediate risk group, but toxicity is clearly higher in the BCG group.

BCG induction therapy and/or BCG + maintenance has never been compared to TUR + immediate instillation of chemotherapy. A better definition of intermediate risk is needed along with specific trials comparing the two approaches.

For those with high risk bladder tumors, BCG + maintenance (as in the SWOG protocol) is the treatment of choice, although the exact number of induction courses, maintenance schedules and BCG’s association with intravesical chemo is still unclear.

BCG is considered the conservative treatment of choice for those in the high risk category; in the absence of randomized trials comparing it to cystectomy, a literature review reveals only one out of seven series showing that immediate cystectomy gives a significant survival benefit when compared to delayed cystectomy after treatment failure. The cause-specific survival of these series showed no difference between both approaches:

BCG failure+delayed cystectomy - 78.6% survival at 5 years

Immediate cystectomy – 84.4% survival at 5 years

Controversy remains over the best time to resort to salvage cystectomy in case of BCG failure. In cases on non-response of high risk tumors to BCG, the progression rate is high, with mortality at five years ranging from 40-66%. Clinical non-response to BCG at 3 months was a good predictive factor for progression.

High risk:

G3 or T1, CIS or prostate involvement plus clinical non response at 3 months: progression to T2 or higher in 72.6% of cases

Intermediate Risk

G1-2 Ta, no CIS, no prostate involvement plus clinical non response: progression occurred in 35%

Any category plus clinical response at 3 months: progression occurred in 10.6%.

High risk patients who do not respond to BCG at 3 months should be offered cystectomy.

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Which patients treated with BCG do better: Those with or without side-effects? A.P.M. van der Meijden, MD, PhD Jeroen Bosch Hospital, ‘s-Hertogenbosch, The Netherlands

OBJECTIVES: Previous publications have suggested that patients developing local and/or systemic side effects to Bacillus Calmette-Guerin (BCG) have a better clinical result, however it is necessary to determine if toxicity is responsible for improved efficacy.

METHODS: After transurethral resection, intravesical instillations of BCG were given during a 6-week induction course followed by 3-weekly maintenance courses at 3, 6, 12, 18, 24, 30 and 36 months. The prognostic importance of delaying or stopping BCG due to local and/or systemic side effects was assessed in 487 patients.

RESULTS: Patients with local BCG side effects had a significantly longer time to first recurrence, suggesting that side effects are related to efficacy. However patients with a better outcome remain on study for a longer period of time and receive more BCG, thus increasing their risk to develop side effects. To prove whether toxicity is responsible for improved efficacy, the prognostic importance of toxicity occurring prior to the 6 month instillations was assessed using

the landmark method. Neither local nor systemic BCG toxicity prior to 6 months was related to subsequent recurrence. CONCLUSIONS: While a correlation between BCG toxicity and efficacy exists, this study does not confirm that BCG toxicity is actually responsible for an improved outcome.

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New Agents in the Treatment of superficial bladder cancer M.A. O’Donnell, MD, University of Iowa Health Care, Iowa, United States

New intravesical treatments and modifications of older protocols have recently emerged which deserve to be considered in the adjuvant treatment of superficial bladder cancer.

Intravesical, cytotoxic chemotherapy

Optimization of Mitomycin C

Most critical aspect of clinical response is drug concentration rather than dose or indwelling time

Drug dilution can be minimized by:

-pre-treatment dehydration of the patient

-complete emptying of urine (verified by bladder scan)

-urinary alkalization

-earlier initiation of treatment administration

Using these techniques, the improvement of clinical response at 4 years went from 23% to 42%

Advances in depth of penetration of Mitomycin C

-Electromotive therapy (iontophoresis)2

-Intra-cavity microwave hyperthermia (SynergoTM)3 - this new treatment is showing impressive results as first-line chemoablation as well as for T1, G3 tumors and in cases of BCG failures.

-Upregulation of key intracellular enzyme quinone reductase - dietary modification (increased consumption of brassica vegetables such as cabbage and broccoli)5, 6

Intravesical Gemcitabine-now entering phase II trials 7,8

-used in case of BCG or previous MMC failure with favorable results, response rates exceeding 50% at 3 months (with drop off after that)

-lower toxicity profile than most commonly used agents

Strategies to maintain a complete response with re-treatment or combination with MMC are underway.

Intravesical Immunotherapy

Optimization of BCG therapy

SWOG 8507's study using post-induction maintenance therapy (see drlammsprotocol) for 3 years has shown clear improvement over the 6 round induction course, lessening both recurrence and progression.9

Whether this is the optimal schedule is still uncertain; two large meta-analyses have shown that a minimum of one year of BCG maintenance provides both significant protection from progression and superiority over intravesical chemotherapy.10,11 Also, reduced dose BCG regimens are emerging which show efficacy with the added benefit of reduced toxicity. 12

However, some high risk tumors subtypes may have less response to reduced BCG. An alternative may be to administer BCG every other week, called "slow rate" dosing.13

Other active agents in BCG failures are mycobacterial DNA cell wall extracts, in trials now for CIS. 14

BCG + Interferon-alpha (IFN-a)

-50% durable disease remissions over two years

-active against previous BCG failures15

-good tolerability and safety profiles16

The potential for combining chemotherapy and immunotherapy seems attractive based on trails using sequential treatments.17,18 It may prove worthwhile to use one dose of chemo after TUR, followed by optimized BCG treatments 2-3 weeks later.

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Session 4: Advanced Bladder Cancer

Chair:P.G.Harper, MD, Guy’s Hospital, London, United Kingdom

What to do when radical cystectomy is not radical

D.P.Petrylak, MD, PhD, Colombia Uinversity, NY, NY, USA

The year 2003 saw approximately 57,400 new cases of bladder cancer in the U.S. Cystectomy remains the gold standard for those with muscle invasive bladder cancer, but the 5 year survival rates are low when lymph nodes or perivesical fat have been invaded, ranging from 5-30%. Lymph nodes are involved in 13% of T1 tumors, 20% of T2, 24% of T3a, 42% T3b and 45% of T4 tumors.

The integration of either neoadjuvant or adjuvant chemotherapy with cystectomy has not yet been clearly defined. Of 8 randomized trials comparing chemo+cystectomy to cystectomy alone, 6 trials showed no statistical benefit, while two trials showed a survival benefit. A randomized trial comparing cystectomy alone to cystectomy+M-VAC demonstrated an improved survival for the chemotherapy arm, especially for those who had a complete response (stage P0).2 A recent European trial achieved a 6% survival advantage using CMV (cisplatin, methotrexate and vinblastine).3

The role of adjuvant therapy is less clear. Past trials have not provided sufficient statistical power or efficiently designed drug protocols. Currently, an EORTC/SWOG trial is comparing adjuvant M-VAC or gemcitabine to treatment at time of progression.

Bladder sparing approaches are designed to integrate chemotherapy and radiation therapy with TUR. The 'combined modality' approach may be appropriate for the elderly and/or those with serious co-morbidities who may not be able to withstand radical surgery [or those who refuse cystectomy].

Sternberg's team in Rome evaluated pre-operative M-VAC in 104 patients with T2-T4 disease; of the 94 people who were restaged, 49% achieved P0 status [complete response of tumor], 51% of those who had a complete response are still alive with an intact bladder. 4,5

Shipley and associates used a sequential regimen of two cycles of CMV followed by radiation therapy using cisplatin as a

radio-sensitizer. Those who did not respond underwent immediate cystectomy, responding patients underwent further combined chemo/radiation therapy. The 5 year survival rates was 54%, with 36% of patients achieving bladder preservation.6

The Southwest Oncology Group studied the efficacy of 5FU and cisplatin+radiotherapy for those with muscle invasive bladder cancer; unfortunately the 5 year survival rate was only 32%.7

The EGF [epidermal growth factor] receptor is present in up to 70% of invasive bladder cancers, while the Her-2 gene is over expressed in up to 25% of primary tumors and 50% of metastatic tumors. At the present there are no molecular markers (or standard way to test them) or imaging techniques sensitive enough to predict which patients are appropriate for bladder preservation. SWOG is currently evaluating biomarkers [p53, RB, MDR, EGF, Her-2] and imaging techniques such as PET scanning to predict who will obtain a complete response to neoadjvant carboplatin, gemcitabine and Taxol.

Those with T2 tumors were the best responders to the combined modality approaches, with a 5 year survival of 45-63%. A superficial relapse occurred in 26-43%. Squamous cell tumors or adenocarcinoma of the bladder were contra-indicative to multi-modality treatment [with cystectomy most often advised].

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Current treatment approaches in advanced bladder cancer P.G.Harper, MD, Guy’s Hospital, London, United Kingdom

Metastatic bladder TCC (transitional cell carcinoma) has an aggressive course, with survival of 3-6 months without treatment. The addition of chemotherapy after cystectomy using cisplatin-containing combination chemotherapy-with M-VAC as the gold standard these last 15 years-has extended survival to 12-16 months, with a response rate ranging from 40-70%. However, long term surival is low (3.7% at six years) with toxicity and number of visits per cycle remaining problematic. 1,2,3

Newer drugs are in trails in an effort to improve outcome and quality of life; these include gemcitabine/Gemzar, paclitaxel/Taxol, docetaxel/Taxotere and ifosfamide.4-10

Von der Masse and colleagues compared gemcitabine + cisplatin with M-VAC in a large, randomized phase III trial; median survival was 13.8 for the GC arm and 14.8 for the M-VAC arm, survival at 18 months was 37% vs 38%, with GC having a significantly better safety profile/tolerability. On the basis of this trial, Gemcitabine+cisplatin has now become the new gold standard treatment for metastatic bladder cancer.8

Phase I and II trials are now comparing gemcitabine plus taxane(s) with or without a cisplatin analogue (related drug) to M-VAC. 11-14 Cisplatin+Taxol and Cisplatin+Taxotere are also under investigation; a recent phase III trial showed that M-VAC was more effective than cisplatin+Taxotere.15

For people who co-morbidities or renal insufficiency, Carboplatin based combinations may be considered; ongoing trials suggest that although the G/cisplatin combination scores better, gemcitabin+Carboplatin is a less toxic, effective regimen

for this population. 16 Taxol+Carboplatin has been tested in several trials but had a substandard survival rate (9.5 months).17

The stratification of patients according to risk factor are needed to avoid bias in the results of future trials. The use of novel prognostic markers in future trials will define their role in clinical outcome, and could potentially help to design individualized chemotherapy regimens. One ongoing trial is randomizing people with postive, over-expressed p53 [thought to be a risk factor for recurrence] to observation after cystectomy or cystectomy followed by M-VAC.18 Monclonal antibody therapies are new, targeted approaches with Trastuzumab (Herceptin) and gefitinib (Iressa) currently being investigated for use in metastatic bladder cancer. A recent phase I trial demonstrated that the use of adenovirus-mediated p53 transfer [gene therapy] is safe, feasible and biologically active. 19

Although there have been no concrete advances in 15 years, newer therapies with less toxicity may begin replacing M-VAC without compromising survival.

Phase II Study of Cisplatin, Gemcitabine, and Gefitinib in Patients With Metastatic Transitional Cell Carcinoma of the Urothelium recruiting

Phase II Study of Trastuzumab (Herceptin), Paclitaxel, Carboplatin, and Gemcitabine in Patients With Locally Recurrent or Metastatic Urothelial Carcinoma Overexpressing HER2 recruiting

Phase II trial to study the effectiveness of combining pemetrexed disodium with gemcitabine in treating patients who have advanced cancer of the urothelium not yet recruiting

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Adjuvant chemotherapy in muscle invasive bladder cancer: Current concepts

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Therapy for muscle invasive bladder cancer can be divided roughly into bladder-sparing and non-bladder-sparing approaches, with the gold standard being cystectomy+lymphadenectomy. Peri-operative chemotherapy is still evolving; the most recent data show a survival advantage with neo-adjuvant (pre-op) chemotherapy.

Rationale behind the use of pre-or post-operative chemotherapy include:

*TCC is chemosensitive, the complete response rate in metastatic disease ranges from 11-25% (according to phase III studies)

*Long term cure has been observed in some cases of metastatic disease

*chemotherapy benefits other cancers with similar metastatic risk and chemosensitivity (ie: breast and colon)

* Long term cure for those with lymph node involvement - incurable by surgery alone - has been seen with chemotherapy followed by cystectomy and lymphadenectomy

Multiple randomized trials of neo-adjuvant chemotherapy have investigated a spectrum of drug regimens; the largest randomized trial in the literature , conducted by The Medical Research Council/European Organization for the Research and Treatment of Cancer (MRC/EORTC) compared neoadjuvant CMV (cisplatin,methotrexate, vinblastine) to a control group that received no chemo before treatment; time to progression was improved by 8%, the 3 year survival rate was improved by 5.5%; the median survival was 44 months with treatment vs. 37.5 for those who received no chemotherapy. However, when the trail was updated in 2002 after a median of seven years, a statistically significant improvement in survival was seen (p=0.048, hazard ratio of 0.85,CI 0.72-1.0).1

A second large, co-operative group study from the Southwest Oncololgy Group (SWOG) showed superior survival with neo-adjuvant M-VAC for 3 cycles vs. cystectomy alone for muscle-invasive disease, with median survivals of 6.2 years for the chemotherapy group vs. 3.8 years for cystectomy alone, and 5 year survivals of 57% and 42% respectively. 2
*Several other randomized trials failed to show a benefit for neo-adjuvant chemotherapy, however these studies had shortcomings such as inadequate number of enrollments, premature closure or sub-standard drug regimens.

A recent world-wide meta-analysis examined the use of neo-adjuvant chemo; a significant survival benefit was seen in those who underwent cisplatin-containing regimens (HR 0.87,p=p016), with no benefit observed in those who had single-agent cisplatin.3

Adjuvant (post-operative) chemotherapy has been studied in five randomized trials, with two of these suggesting a survival benefit for adjuvant chemotherapy over cystectomy alone. 4-6 Although there is insufficient data available about the efficacy of adjuvant chemo, it is assumed that adjuvant treatment is equally effective as neo-adjuvant treatment with M-VAC or GC.

There is sufficient evidence from the MRC/EORTC and SWOG trials, along with the meta-analysis, to support the use of neo-adjuvant chemotherapy in the treatment of muscle invasive bladder cancer for those who are candidates for cisplatin-based therapies.

Ongoing clinical trials are evaluating the use of adjuvant chemotherapy in the US and Europe, and will hopefully give some clearer answers about this approach in the near future.

*[see also: chemo controversy]

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Overview of novel agents

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Thanks to advancements in the understanding of molecular biology and the new drugs which have resulted from this, a new era is emerging with new anti-cancer agents that inhibit many of the 'hallmarks of cancer."1

Epidermal Growth Factor

Both tyrosine kinase inhibitors (TKI) and monoclonal antibodies have been developed to combat the malignant potential of the EGF axis; Trastuzumab [Herceptin] and gefitinib [Iressa] have been evalutad, both with limited success (the latter gave a complete response in 3% of patients). Pertuzumab, a new monoclonal antibody, has a different mechanism, blocking HER-2 association with other HER family members (HER1/EGFR, HER3 and HER4), inhibiting intracellular signaling. The over-expression of the HER-2 gene is not necessary for the anti-tumor activity of this new agent.2 HER-2 overexpression has been seen in up to 50% of metastatic tumors.

COX-2: Eicosanoid metabolism

Cyclo-oxygenase-2 (COX-2) is a known cancer promoter; inhibition of this enzyme may prove to be a successful chemo-preventative agent in the fight against TCC. COX-2 inhibitors, successful in treating familial colonic polyps, is being investigated in Phase III trials for the prevention of superficial recurrences.4,5

Angiogenesis

The developement of most cancers-including TCC- depend up the growth of new blood vessels to promote tumor growth.6 Vascular endothelial growth factors (VEGF) inhibition are a reasonable target in the fight against TCC, drugs like Bevacizumab are being tried. Angiogenesis can also be inhibitied by turning off pathways that promote angiogenesis (Nuclear factor kappa B and EGFR), however, determination of factors that give tumors the ability to grow independent of angiogenesis inhibition must be considered. 7

Frequent, low daily doses of IFN (interferon) have also been shown to lower micro-vessel density (MVD).

Nuclear Factor kappa (NF-kappa B)

NF-kappa B is a transcription factor that promotes many of the hallmarks of cancer such as invasion, evasion of apoptosis, angiogenesis and metastasis. The use of proteasome inhitors has been successful in the treatment of myeloma, 8 presumably by inhibition of NF-kappaB, and preclinical work has shown the presence of this factor in cinical specimens. 9 Ihibition of NF-kappa B has been shown to retard tumor growth in othortopic bladder cancer models.10

New chemotherapeutic agents

Any advancement in systemic therapy made thus far is thanks to this type of therapy (cytotoxic drugs). These agents impact inhibit replication. Pemetrexed [Alimta] inhibits cellular replication by impeding folate metabolism and thus RNA and DNA synthesis. This new agent has shown activity in TCC, with a 29% response.10

Phase II trial to study the effectiveness of bortezomib in treating patients who have advanced or metastatic transitional cell cancer of the bladder, renal pelvis, or ureter. recruiting

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Future management of advanced bladder cancer

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new paradigm of molecular prediction

Bladder TCC is a complex malignancy with the capacity to differentiate along different cellular pathways including transitional cell, squamous and adenocarcinoma. This makes them much more difficult to target with chemotherapy. In addition to histological heterogeneity [heterogeneous-consisting of dissimilar or diverse ingredients or constituents: m-w.com], bladder cancer also exhibits molecular heterogeneity, and variably expresses genes and oncogenes including p53, p16, p21, RB, Ras, erb-B2, and EFGR among others. Genes that code for glutathione, the metallothioneines, thymidylate synthase (TS), EGFR, and the multi-drug resistant phenotype (MDR) are all expressed in bladder cancer and have been shown to have biological activity.

Data suggests that some of these genes may confer increased responsiveness to chemotherapy; for example the studies being done with p53 at USC Norris Cancer Institute (however, data from Memorial Sloan Kettering in NYC and out of Toronto do not share the same conclusions). In addition to prediction of chemo-sensitivity, these genes could be used to devise more tailored, individual therapies for patients, stratified according to careful molecular profiling. This approach has the potential to overcome the most pressing problem in oncology today: intersubject variation of drug response and toxicity (there is evidence that African-American and Latino population responds differently to common chemo-agents).

Glutathione expression has been correlated to chemo response; DPD overexpression predicts tumor non-response; a mutated p53+an absent p21=10% survival at ten years, regardless of the original stage.

An international randomized clinical trial is testing the efficacy of post-operative M-VAC for those with T1, T2 tumors who test postive for the p53 marker. Such an approach represents a new paradigm in clinical trial design.

Phase III Randomized Study of Methotrexate, Vinblastine, Doxorubicin, and Cisplatin Versus Observation Alone Based on p53 Gene Status in Patients With Organ Confined Transitional Cell Carcinoma of the Bladder Who Have Undergone Radical Cystectomy and Bilateral Pelvic Lymphadenectomy

Novel Therapeutic Approaches

Several new drugs have been introduced into routine clinical use during the last decade, including gemcitabine, paclitaxel (Taxol), docetaxel (Taxotere), and isfosfamide. A number of others have been tested but failed to show sufficient benefit, including gallium nitrate and trimetrexate. Controversy arose with the use of Carboplatin, alone or in combination, due to the evidence of inadequate response and survival. SWOG is now assessing the use of ininotecan based on preliminary Japanese data. Phase II trials are also studying the the novel antimetabolite, pemetrexed.

The combination of chemotherapy with novel biological agents targeting cell surface growth regulators such as EGFR and erb-B2 are also in clinical trials. The intitial results of the combination of trastuzumab+chemotherapy has not shown improved outcome, but this study is the first to evaluate such an approach; in the next generation of clinical trials, molecular typing of bladder cancers along with innovative clinical trials will help to clarify the use of such novel agents. In the near future it will become crucial for clinicians to understand and integrate molecular biology into trial design and clinical practice.

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