Biomarkers - Prognostic and Predictive Indicators

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EFGR [epidermal growth factor-receptor and bladder cancer: French researchers report in 2004: "This marker yields significant prognostic information in addition to stage and grade and may be of value for the clinical management of superficial and invasive bladder carcinomas. The pattern of EGF-R immunostaining and its association with tumour progression makes it a candidate for antigrowth factor therapy." PubMed Abstract

Molecular markers for predicting recurrence, progression and outcomes of bladder cancer (do the poster boys need new posters?)

Current Opinion in Urology. 14(5):277-286, September 2004. Duggan, Brian a; Williamson, Kate b

Update: 2004; Recent findings: In the last year, DNA microarray assessment has revealed several interesting molecular markers such as p33ING1 and DEK. Parallel 'conventional' single-pathway research has focused on new novel markers such as HER2/neu, survivin and matrix metalloproteinase 2 (MMP-2). Molecular markers that have a long-standing association with bladder cancer progression such as p53, E-cadherin and Ki-67 have been reviewed by both single-marker studies and by microarray studies and their status remains important.

Summary: It is an exciting time in the molecular biology research of bladder cancer as the focus changes to assess the global genetic and protein expression within tumour cells. From such a wealth of information it is likely that molecular markers will make the translation from benchside to bedside.PubMed

Integrating basic science and clinical research in bladder cancer: update from the first bladder Specialized Program of Research Excellence (SPORE). Current Opinion in Urology. 14(5):295-300, September 2004.

Highshaw, Ralph A a; McConkey, David J b; Dinney, Colin P a

Summary: Targeted therapy against epidermal growth factor receptor has become one of the primary focuses of the genitourinary SPORE[Specialized Program of Research Excellence] in bladder cancer. The SPORE grant scheme is designed to encourage rapid development of new and innovative cancer research in areas of high priority, in this case bladder cancer. The SPORE has facilitated the advancement of novel epidermal growth factor receptor-targeted therapy, such as the monoclonal antibody IMC-225 and the tyrosine kinase inhibitor ZD1839 (Iressa), from the laboratory to clinical trials. The integration of these new biological agents in combination with chemotherapy, in order to abrogate the progression of advanced bladder cancer, is the prime directive of our current phase II Iressa/docetaxel trial.

Molecular analysis of transitional cell carcinoma using cDNA microarray. The incidence of transitional cell carcinoma (TCC), the fourth most common neoplasm diagnosed in men, is rising. Despite the development of several noninvasive diagnostic tests, none have gained full recognition by the clinicians. Gene expression profiling of tumors can identify new molecular markers for early diagnosis and disease follow-up. It also allows the classification of tumors into subclasses assisting in disease diagnosis and prognosis, as well as in treatment selection. In this paper, we employed expression profiling for molecular analysis of TCC. A TCC-derived cDNA microarray was constructed and hybridized with 19 probes from normal urothelium and TCC tissues. Hierarchical clustering analysis identified all normal urothelium samples to be tightly clustered and separated from the TCC samples, with 29 of the genes significantly induced (t-test, $P<10(-5)$) in noninvasive TCC compared to normal urothelium. The identified genes are involved in epithelial cells' functions, tumorigenesis or apoptosis, and could become molecular tools for noninvasive TCC diagnosis. Principal components analysis of the noninvasive and invasive TCC expression profiles further revealed sets of genes that are specifically induced in different tumor subsets, thus providing molecular fingerprints that expand the information gained from

classical staging and grading. PMID: 14576834 [PubMed - indexed for MEDLINE] Oncogene, England; Vol 22, No 48 (Oct 23, 2003): pp. 7702-10 QBI Enterprises Ltd, PO Box 4071, Nes Ziona 70400, Israel. Orna Mor, Ofer Nativ, Avi Stein, Lion Novak, Dana Lehavi, Yoel Shiboleth, Ada Rozen, Eva Berent, Leonid Brodsky, Elena Feinstein, Ayelet Rahav, Keren Morag, Daniel Rothenstein, Nurit Persi, Yoram Mor, Rami Skaliter, Aviv Regev

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The research continues to show promising results, yet no biomarker has yet to be used in clinical, everyday practice.

Of note: Predictive value of cell cycle biomarkers in nonmuscle invasive bladder transitional cell carcinoma.

The purpose was to determine whether the combined

expression of p53, p21, p27 and pRB is associated with

outcomes of patients with nonmuscle invasive bladder

transitional cell carcinoma. Conclusion:

They conclude that combinations of p53, pRB, p21 and

p27 had cooperative/synergistic effects stratifying

patients into different risk groups. Higher total

numbers of altered biomarkers were independently

associated with an increased risk of disease

progression and death. Prospective trials are

necessary to usher bladder cancer management into the

age of molecular biomarkers.

Journal of Urology Volume 177, Issue 2, Pages

481-487 (February 2007). PUBMED

Update Dec. 2005: Future directions in bladder cancer research- Genetic Markers Gigliola Sica- Chairman Institute of Histology and Embryology

Faculty of MedicineCatholic University of the Sacred Heart Rome: A comprehensive look at markers today, WebCafe conference review

Updates Dec. 2004- Usefulness of CA 125 as a preoperative prognostic marker for transitional cell carcinoma of the bladder- see below

Scientists Begin Validation Study of Test to Detect Recurrence of Bladder Cancer - By examining genetic changes in DNA obtained through urine samples, the test, if successfully validated, will provide a sensitive and non-invasive method of screening for bladder cancer recurrence: more research updates on WebCafe: click here

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Campbells Urology, an esteemed textbook for urologists, states in the preface of it's 1997 edition; "As we enter the 21st century it seemed appropriate to begin the book with the principles of molecular genetics."

The study of biomarkers, or chromosomal abnormalities that can possibly predict how a person’s disease may progress or respond to treatment, falls under the category of chemoprevention as scientists hope that the end result of these studies will provide an aid in early detection and screening, which could hopefully make a dent in the statistics re: bladder cancer specific deaths. The biomarker must be expressed differently in normal and high-risk tissue, with clear evidence of progression from normal tissue to biomarker to cancer and, ideally, should appear early in carcinogenesis. If the use of biomarkers proves to be a tool for achieving successful preventive intervention, this would support the possibility that a preventive agent that could reverse these molecular events (or suppress their consequences) for one tumor site may be effective in preventing a variety of tumors. The development and validation of biomarkers are important to the success of testing chemopreventive agents. 1

Examples of biomarkers include include genetic markers (eg, nuclear aberrations [such as micronuclei], gene amplification, and mutation), cellular markers (eg, differentiation markers and measures of proliferation, such as thymidine labeling index), histologic markers (eg, premalignant lesions, such as leukoplakia and colonic polyps), and biochemical and pharmacologic markers (eg, ornithine decarboxylase activity). 1

This aspect of urology/oncology is currently one of intense research efforts. The ultimate goal is to find a marker that can reliably detect occult disease.2At the present time none of the markers tested is elevated in more than 50% of patients. The use of biomarkers has not yet been incorporated into standard staging procedures, and although great headway is being made in the field of biomarker studies, at this point in time pathological assessment of stage and grade is still the best index of prognosis in common use.

Many recent investigations have been conducted to determine whether new biological markers will help predict disease progression and potential clinical applications of these tumor markers are under active investigation. Recent attention has focused on which tumor markers may predict the responsiveness of a particular bladder cancer to systemic chemotherapy. Some of these new predictive and prognostic markers include DNA ploidy, S-phase, Ki-67, Her2/neu (c-erb B-2) , p53, p21, the retinoblastoma (Rb) gene, MDR-1, bcl-2, cell adhesion molecules, blood group antigens, tumor associated antigens, proliferating antigens, oncogenes, peptide growth factors and their receptors, tumor angiogenesis and angiogenesis inhibitors, and cell cycle regulatory proteins. Beta human chorionic gonadotropin (ß-hCG), carcinoembryonic antigen, CA-125, CA 19-9, and others have been evaluated and shown to correlate with clinical response to chemotherapy (not a complete list).. 3 4 5 9 G Actin and Ki67 have indicated response to BCG and radiation, respectively.6 7

The most discussed chromosomal biomarker of all is the p53 protein, a tumor suppressor gene on chromosome 17p. Between 1993 and 1996 over 4,000 articles on this subject were published.8 A wealth of studies seems to confirm that the p53 protein, if mutated and overexpressed in cancerous cells, is an indication of a potentially aggressive condition. 9

It’s been shown that both grade and stage of (invasive) bladder cancer are related to p53 alterations.10 Mutations in the p53 gene are observed in 65% of CIS cases and 51% of muscle invasive TCC, while only 3% of papillary Ta tumors show mutations. 11

Mutations in the p53 gene can be detected in tissue sections by immunohistochemistry. Since the wild-type p53 gene has a short life, immunostaining of normal urothelium with p53 monoclonal antibodies is negative. When mutations in the p53 gene occur, the mutated proteins aggregate in tetrameric and pentameric macromolecules of longer life. The result is an accumulation of p53 protein that provides a positive immunostaining reaction. The reaction is observed in the nuclei of tumor cells affected by these events. The role of the immune system in neutralizing the invasive potential of CIS is unknown but may explain why a significant proportion of CIS fails to invade.11

The function of p53 is critical to the way that many cancer treatments kill cells since radiotherapy and chemotherapy act in part by triggering cell suicide in response to DNA damage. This successful response to therapy is greatly reduced in tumours where p53 is mutant so these tumours are often particularly difficult to treat. It is hoped that better understanding of p53 can guide the developement of new treatments for cancer. Scientists are beginning to unravel some of the mysteries and in the test tube at least, are beginning to find ways to make these damaged p53s work again. Such discoveries could potentially offer a powerful and selective new way of treating cancer.12

How should P53 status be used during decision making for patients with superficial transitional cell carcinoma of the bladder?

A number of retrospective studies have now demonstrated the prognostic value of P53 status for patients with superficial transitional cell carcinoma of the bladder. Patients with greater than 20 percent nuclear staining for P53 are at higher risk for tumor progression and recurrence. P53 mutations are relatively uncommon in patients with low grade low stage disease and analysis of P53 status is unlikely to play a significant role in decision making about this group of patients. However, in patients with high grade papillary or T1 disease, P53 status can be used with other prognostic parameters when deciding between intravesical vs. more radical forms of therapy. However, we must acknowledge that the optimal use of P53 status has not been defined. Virtually all studies reported to date have been retrospective and prospective evaluation and confirmation is greatly needed. http://www.nums.nwu.edu/urology/physicians/FAQs/p_bldrcnc.html

New data coming in regarding another biomarker, the p21 gene, is showing that people with p21-positive tumors have a decreased probability of tumor recurrence.13

An article from Journal of the National Cancer Institute, July 15, 1998, discusses a multi-centre, randomised clinical trial using p53-status of tumour cells and other molecular markers like p21 to guide treatment decisions in bladder cancer patients, one of the first of it’s kind.

The research team from USC/Norris Comprehensive Cancer Center conducted a study on 242 patients with locally confined bladder tumors who were followed for an average of 8.5 years. Analysis was done of of the p21 protein and it’s interaction with the p53 protein. Results of the study indicated that patients with p21-positive tumours survived disease-free significantly longer than those patients with p21-negative tumours. Furthermore, it was shown that the way the p21 and p53 proteins interact with each other can give a very good indication of which patients must be considered at high risk for recurrence.

The article stated that p53 is known to be a primary regulator of p21, since genetic changes in p53 may lead to loss of

p21 expression and function. This in turn leads to unregulated cell growth, and is thought to contribute to the aggressive behaviour of some tumours. "We reasoned that if p21 is [positively] expressed despite alterations in p53, then cell cycle control might be maintained and the tumours would be less likely to progress," said Dr. Richard Cote, M.D., Ass. Prof. of Pathology and Urology, and researcher at Norris. "Our hypothesis seems confirmed by this study.”

Patients with p53- altered/p21-negative tumors demonstrated a higher rate of recurrence and worse survival compared with those with p53-altered/p21-positive tumors. Patients with p53-altered/p21-positive tumors demonstrated a similar rate of recurrence and survival as those with p53-wild type tumors.13

John Stein, M. D., Assistant Professor of Urology, an expert on surgical approaches to bladder cancer and a colleague of Cote’s at USC stated; "Molecular markers will allow us to manage patients with a clearer idea of the benefits of treatment in that individual. This represents a greatadvantage to physicians and patients.”

July 15, 1998 Journal of the National Cancer Institute

Memorial Sloan Kettering Cancer Center in NYC has also conducted a study on the usefulness of p53 to guide treatment approaches. The findings of Herr and colleagues in published 1999 suggest that the bladder may be preserved for up to 10 years in patients with tumors confined to the bladder (stage T2) who lack detectable p53 if they respond completely to neoadjuvant chemotherapy. The authors conclude that patients with T3 bladder tumors or T2 p53 positive tumors are best treated currently with cystectomy. 14

The loss of expression of the retinoblastoma gene (Rb) on chromosome 13q (3) has also been associated with malignancies including bladder cancer.

In 1992 Logothetis and fellow researchers from MD Anderson concluded that “The high frequency of Rb alteration in locally advanced bladder carcinomas, plus the fact that a significant correlation could not be found between the Rb status and other known prognostic markers in this preliminary study, suggests that altered RB expression may be an independent prognostic marker of tumor progression in bladder cancer.”15

In 1998, Cote and associates at Norris concluded that tumors altered in both p53 and pRb have significantly increased rates of recurrence and lower survival compared to those with no alterations in either p53 or pRb; patients with alterations in only one of these proteins had intermediate rates of recurrence and survival. These results suggested that: (a) bladder cancers with high pRb expression do not show the tumor suppressor effects of the protein; and (b) alteration in both p53 and pRb may act in cooperative or synergistic ways to promote tumor progression.16

Another biomarker, bcl-2, is an apoptosis regulator; when production of bcl-2 is deregulated, overexpression acts to prevent apoptosis and the cells prolonged survival provides additional opportunity to acquire futher abnormalities. Recent findings from Dr. Mayake's team in Japan suggest that, if it is overexpressed, Bcl-2 prolongs cell survival under unfavourable conditions encountered in the metastatic process, resulting in the enhanced metastatic potential of bladder cancer.17

The same researchers have reported other findings which suggest that the expression of Bcl-2 in bladder cancer cells interferes with the therapeutic effects of cisplatin through the inhibition of the apoptotic pathway.18

Memorial Sloan - Kettering Cancer Center-July 2000: MSK investigators have pinpointed a protein that may identify which patients with bladder cancer are likely to fare well with standard treatment, as opposed to those who might need more aggressive therapy. The protein, E2F-1, may be a useful marker to help doctors determine the most effective course of treatment for each patient. MSK physicians are also using a new combination chemotherapy -- with ifosfamide, taxol and platinum, also known as TIC-- that appears to be more effective and have fewer side effects that M-VAC, the standard therapy.

MDR-1 (Multiple Drug Resistance) expression in cancer cells is associated with resistance to natural product chemotherapeutic agents such as Taxol, Doxorubicin, and Etoposide, and detection of MDR-1 can play a critical role in the selection of a treatment regimen. Benson and colleagues from Columbia University stated that the ability of flow cytometry to detect and quantify the expression of MDR-1 may allow for the early detection of chemotherapy resistance in TCC patients treated with systemic and intravesical therapy.19

Another important predictive marker is MRP. This marker is associated with resistance to commonly used drugs in treatment of bladder cancer such as platinum analogs, vinblastine, etoposide, doxorubicin, and other drugs which may be conjugated with glutathione.20

Kubo and fellow researchers from Japan reported that ‘The intrinsic or acquired resistance of urothelial cancer to chemotherapy is one major obstacle to successful treatment’. Their study showed that 17 of 33 bladder tumors (51.5%) expressed more than 2-fold the MRP mRNA levels of drug-sensitive human KB cells, and they concluded that MRP may be one mechanism responsible for intrinsic drug resistance in low-grade urothelial cancer.21

A recent article by Hemstreet and colleagues from the University of Oklahoma discussed the use of DMSO to modulate biomarker expression of G-actin, DNA aneuploidy, and p300 tumor antigen, which were evaluated prior to and immediately following treatment with BCG on 25 people. Excluding patients who did not respond to BCG recurrence correlated with persistent abnormal G- actin findings. Of patients who were G-actin negative following therapy, only 25% recurred during follow-up in contrast to 67% in patients who were positive. The authors concluded that Cytosolic G-actin levels can be an important intermediate end point marker for chemoprevention. 6

Superficial, low grade papillary tumors are not routinely tested for biomoarkers, as it isn’t considered cost effective (not proven to save lives in the long run) and the efficacy is questioned. The testing of biomarkers is not routine and still considered experimental, although the flood of data on p53 has started to influence even the most isolated urologists.

For superficial cancers, abnormal p53, P21 or Ki67 does not predict how a tumor will respond to BCG, both negative and positive tumors respond well.22 Also, abnormal p53 does not guarantee that a tumor will progress, it only indicates that there a likelihood; P53 overexpression in the tumor and stage T1 disease before BCG therapy indicates a high risk of disease progression. Furthermore, in the group of patients with residual disease after BCG therapy, p53 status is a better predictor of disease progression than was the actual post-BCG disease stage.23

If a tumor has been determined to be poorly differentiated and high grade, no matter the stage, you might want to ask about what kind of patholgy tests were done, what they showed, whether the Rb, p53 and p21 or any other prognostic/predictive indicators have been analyzed, whether this could or should effect treatment strategy.

Larger prospective studies are needed to evaluate further the independent value of these biological markers in superficial bladder cancer management. It is important that the analysis of the p53 and other biomarkers be done properly, and not all urologists and pathologists are able to interpret the findings correctly.

Biomarkers are also being tested in private labs. For a look at what they are doing for bladder cancer there is a website www.IMPATH.com which has labs in New York, LA and Pheonix. IMPATH is a resource for pathologists, as well as patients. Some of the biomarkers used for analysis of bladder tumors are the Ki-67, bcl-2, MDR-1, the Lewis X blood group antigen, proteins p21 and p53, the retinoblastoma gene and DNA ploidy.

“For poorly differentiated tumors, morphological assessment alone errs so often (in nearly 50 percent of cases overall), that failure to perform immunohistologic studies is difficult to defend ethically or legally. In cases of poorly differentiated carcinomas of prostate/bladder area; Prostate cancer may invade the bladder, and bladder tumors may invade the prostate, but the therapies for these two entities differ markedly. Incorrect therapy resulting from misdiagnosis may lead to fatal spread of the disease” Source; Impath website.

Many patients feel that by educating themselves (and perhaps even their doctor in the process), they can be assured that they will get the best odds in the long run. On the other hand, you have to take into consideration what this information would mean to you, will it change anything in your treatment? Could you rest easy knowing that you have an aggressive condition that needs careful monitoring? If you have put yourself in the hands of a competent team of doctors that you have confidence and trust in, this is also a valid approach. Each individual must find the path that helps him or her cope in the best way possible. For some, it’s knowing every angle no matter how scary. Others may be less comfortable with this information.

In the face of bladder cancer patients advocating for more clinical trials, studies and use of these tests, hopefully more funding will be allocated and we will soon get the clear answers we are wating for.

Here are a couple of links to p53 sites;

http://www.dundee.ac.uk/pathology/p53homepage.htm

This is useful if you follow the two "workshop" links and then the "oral presentations" link.

http://bioinformatics.weizmann.ac.il/hotmolecbase/entries/p53.htm

Some useful links and explanations.

A useful book to help lay people understand the process of a cell’s mutations;"One renegade cell", by Robert A Weinberg. Basic Books; ISBN: 0465072755

Links and book recommended by Steve Miley

Tumor Marker for Bladder Cancer

CA-125 is a well-established marker for ovarian carcinoma. Moreover, peritoneal irritation, whether from infection, a simple paracentesis, inflammation, or tumor of any kind, can cause increases in serum CA-125 levels. As such, routine clinical use of CA-125 as a marker of disease cannot be endorsed, but it remains an area of potential clinical study.

Usefulness of ca 125 as a preoperative prognostic marker for transitional cell carcinoma of the bladder

Increased CA 125 was seen in approximately 11% of patients with high grade or invasive TCC preoperatively. It was more commonly found in patients with locally advanced and lymph node positive disease, and it was associated with overall survival. However, recurrence-free survival was not associated with CA 125. Further studies are required to define the exact role of CA 125 in bladder cancer.

From the Departments of Urology (AC, GM, DS, JPS) and Biostatistics (JC, SG), University of Southern California Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, California. CHANG, ANDY; CAI, JIE; MIRANDA, GUS; GROSHEN, SUSAN; SKINNER, DONALD; STEIN, JOHN P. Journal of Urology. 172(6, Part 1 of 2):2182-2186, December 2004. PubMed

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