SEATTLE CANCER CARE ALLIANCE

Fred Hutchinson Cancer Research Center
UW Medicine
Seattle Children's

UW Medicine

Bladder Cancer Bulletin

JANUARY 2015

Bladder Cancer Among Most-Mutated Cancers

Many new studies have identified mutations in invasive and superficial bladder cancer that hold hope for identifying targets for improving therapy.

Work published in *Nature* from The Cancer Genome Atlas (TCGA) (http://cancergenome.nih.gov) project provided an exhaustive analysis of mutations, changes in gene number, and levels of mRNA. The bladder TCGA was one of the first reports from the comprehensive TCGA effort by the National Cancer Institute (NCI) to characterize the molecular profile of the most common malignancies. Investigators evaluated 131 clinically localized, muscle invasive (T2) urothelial carcinomas, which revealed that bladder cancer is among the most heavily mutated cancers, ranking third behind lung cancer and melanoma.

New Genetic Information May Guide Bladder Cancer Treatment

As might be expected from a heavily tobacco-related cancer, a large number of mutations were identified, many of which involved tumor suppressor genes such as p53 (49 percent) and RB (13 percent). Although many of these mutations have been previously described, some novel mutations were also found. Mutations and alterations of several genes involved in DNA repair were identified, including ERCC2 and ATM (ataxia-telangectasia mutated). This is relevant in bladder cancer because DNA-damaging agents, like cisplatin, are an important part of chemotherapy treatment. Mutations of these and other DNA-repair pathway genes were subsequently found to predict for sensitivity to platinum chemotherapy (see below).

Mutations in many other cancer-related pathways were also described in the bladder cancer TCGA, including activating mutations of HER2 (5 percent), HER3 (11 percent) and fibroblast growth factor receptor (FGFR) genes. Completely novel fusions of FGFR3 with a gene called TACC were found in a small number of tumors, suggesting that this fusion may be important in a subset of bladder tumors.

Mutations in related genes in several pathways including p53 and RB, modification of histones on DNA, and

CONTINUED ON PAGE 2

Current Bladder Cancer Research Studies

SCCA has over 200 clinical trials open for patients and intends to lead the world in translating scientific discovery into the prevention, diagnosis, treatment, and cure of cancer. Open studies are online at www.seattlecca.org/clinicaltrials.

- Radiation Therapy + Chemotherapy for Stage T1 Bladder Cancer (UW 7684): NCT00981656
- Sirolimus + Cisplatin/Gemcitabine for Bladder Cancer: NCT01938573
- AGS15E for Metastatic Urothelial Cancer: NCT01963052
- MPDL3280A for Locally Advanced or Metastatic Urothelial Bladder Cancer: NCT02108652

Contact the research coordinators listed on the website for specific protocols.

Bladder Cancer Among Most-Mutated Cancers p1
Current Bladder Cancer Research Studies p1
Organ-Preserving Therapy for Bladder Cancer p3
General Contacts p4
Bladder Cancer Multispecialty Clinic p4

CONTINUED FROM PAGE 1

tyrosine kinase/PI3 kinase pathways were present in over half of tumors. Mutations in the histone methyltransferase MLL2/KMT2D were seen in 27 percent of bladder cancers. MLL2 mutations have been described in several other tumors, but had not been previously described in bladder cancer. How these mutations may alter bladder cancer biology is unknown but is being explored in animal models at Fred Hutch. One of our researchers, David MacPherson, MD from the Hutch has studied MLL2-mutated lung cancer extensively in mouse models and is now applying his laboratory's experience to bladder cancer. This work can potentially lead to novel targeted therapies in bladder cancer patients carrying this mutation.

Clinical Correlations

Gene Mutations

Immediate applications of these findings were presented at the American Society of Clinical Oncology (ASCO) meeting this year (2014). Van Ellen et al performed sequencing of muscle invasive bladder tumors treated with neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy and correlated the presence of specific mutations with the likelihood of achieving a pathologic complete response (pCR) or only residual CIS (carcinoma in situ). In their analysis, the presence of a mutation of the DNA repair gene ERCC2 in a tumor prior to therapy was predictive of pCR in 100 percent of tumors. This implies that the ERCC2 mutation in tumors makes them extremely sensitive to MVAC, likely because it prevents tumor cells from using repair mechanisms to survive DNA damage caused by cisplatin. Whether the ERCC2 mutation also makes these tumors equally sensitive to other DNA-damaging therapies such as carboplatin chemotherapy or radiation therapy remains uncertain. In the laboratory, the ERCC2 mutation has been found to confer sensitivity to radiation. ERCC2 mutations were present in 12 percent of the TCGA dataset.

In another study, Plimack et al presented similar data from patients treated on a neoadjuvant MVAC study from Fox Chase Medical Center. In this study, the investigators used the Foundation Medicine platform, in which specific exomes of several genes were interrogated. In their study, if a mutation of Fanconi's anemia gene (FANCA),involved in DNA repair, ataxia telangiectasia mutated (ATM), also involved in DNA repair, or retinoblastoma (RB) was present, patients experienced a pCR to chemotherapy. The frequency of ATM in the TCGA dataset was 12 percent, and FANCA was not described as a recurring mutation, but was present in 5 percent of superficial tumors in another sequencing study (Balbas-Martinez).

Mutations in one or more of these components of the DNA repair pathway appear to be present in 25 to 35 percent of tumors. The complete response rate to neoadjuvant chemotherapy in most cisplatin-based regimens was also reported to be 25 to 35 percent. If these analyses are confirmed, the ability to predict benefit for patients receiving neoadjuvant and adjuvant chemotherapy may become a real possibility in the near future.

In addition, these studies have identified potential novel targets, such as FGFR3, to be explored in subsets of bladder cancer patients. Together, these studies emphasize that there is likely no single "one size fits all" approach to addressing the molecular signature of bladder cancer. Finding a way to evaluate biomarkers in real-time will be required to provide more personalized cancer care.

Molecular Profiling Platforms

From the standpoint of molecular profiling, there are many platforms available and in development. The UW-Oncoplex assay (http://tests.labmed.washington.edu/UW-OncoPlex) and Foundation Medicine assay (www.foundationmedicine.com/) are potential ways to leverage mutation findings. Both assays are being adjusted to accommodate the significance of these mutations.

Looking for "Super Responders"

Research regarding the importance of these mutations in localized and metastatic bladder cancer is ongoing at the University of Washington and the Hutch. Investigators are interested in identifying patients who may be considered "super responders," or the small proportion of patients who have been cured of metastatic disease with systemic therapy. Please contact the investigators at the end of this bulletin if you have patients who may be appropriate.

Why This is Important

- Mutations in bladder cancer genes regulating DNA-damage repair are very likely to be predictive biomarkers of platinum-based chemotherapy sensitivity
- This may allow identification of patients most likely to benefit from neoadjuvant and adjuvant chemotherapy
- Mutations in kinase and other pathways may allow novel targeting of these mutations (HER2 and FGFR3) for therapy

Organ-Preserving Therapy for Bladder Cancer

Although radical cystectomy is the most common treatment for localized muscle-invasive bladder cancer, preservation of the bladder is possible in carefully selected patients. Patients with significant comorbidities, advanced age, or poor performance status may not be optimal candidates for cystectomy. Primary therapy with a combination of radiation therapy and concurrent sensitizing chemotherapy may be an alternative.

Accumulated experience from a number of single-institution and cooperative-group trials have demonstrated that chemoradiation following maximal surgical debulking with TURBT to be an effective therapy for muscle-invasive bladder cancer. Approximately 75 percent of surviving patients are able to maintain their bladder, and quality-of-life studies demonstrate that the majority preserve excellent long-term bladder function.

Patient selection is important to identify those most likely to have a good outcome with this approach. The best candidates for bladder preservation are those with:

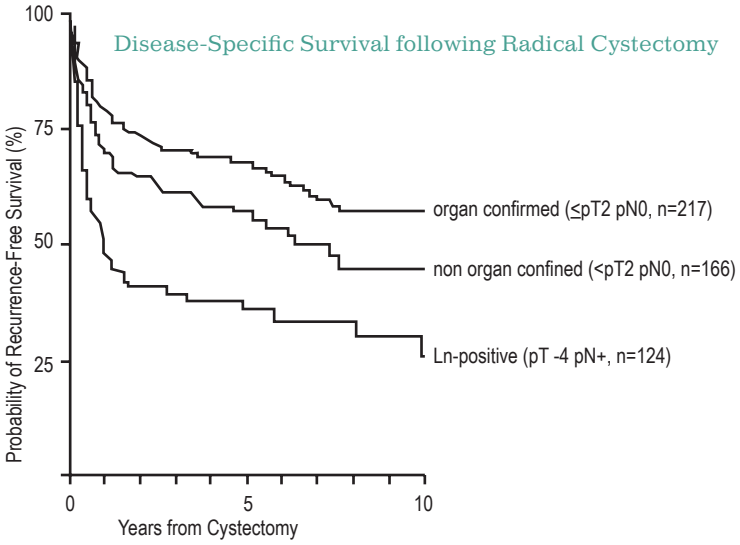
» Solitary muscle-invasive tumors
» Small (<5cm) tumors
» The possibility of complete endoscopic debulking (TURBT)
» Good underlying bladder function
» An ability to comply with close post-therapy surveillance

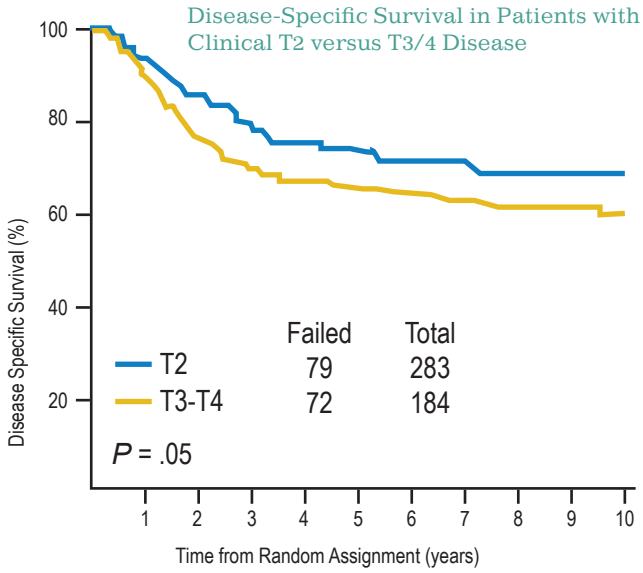
And without:

» Hydronephrosis or nodal metastasis
» Extensive carcinoma in situ

While there is no prospective randomized comparison of surgery versus chemoradiation, rates of five-year progression-free survival comparable to cystectomy have been reported (see figures). A variety of chemotherapy regimens have been found to be effective when used concurrently with radiation, including high-dose cisplatin every three weeks, fluorouracil, mitomycin C, and gemcitabine (refs). For patients who are cystectomy candidates but opt for chemoradiation, a mid-course reassessment after four to five weeks of therapy, with repeat TURBT to assess response, is standard practice. From this, good responders should continue with organ-preservation therapy; poor responders should proceed to immediate cystectomy. Ongoing chemoradiotherapy studies are also available as an alternative to cystectomy for patients with recurrent, non-muscle invasive bladder cancer, with earlier stage disease (see below graphs).

Other organ sparing approaches might include partial cystectomy or TUR alone in the small subset of patients Other organ sparing approaches might include partial cystectomy or TUR alone in the small subset of patients (10 percent) who are rendered disease-free at repeat staging TUR. Bladder sparing treatment approaches require close multidisciplinary care and collaboration in order to appropriately select patients, optimize real-time assessment of disease status, and coordinate all the steps of therapy.





References

1. Comprehensive molecular characterization of urothelial bladder carcinoma. *Nature.* 2014 Mar 20;507(7492):315-22.
2. Van Allen E, et al. Somatic ERCC2 mutations correlate with cisplatin sensitivity in muscle invasive urothelial carcinoma. *Cancer Discovery* (2014 Aug 5, epub)
3. Balbás-Martínez C et al. Recurrent inactivation of STAG2 in bladder cancer is not associated with aneuploidy. *Nat Genet.* 2013 Dec;45(12):1464-9.Plimack et al. Next-generation sequencing to identify molecular alterations in DNA repair and chromatin maintenance genes associated with pathologic complete response (pT0) to neoadjuvant accelerated methotrexate, vinblastine, doxorubicin, and cisplatin (AMVAC) in muscle-invasive bladder cancer (MIBC). Proc ASCO #3548, 2014.

General contacts:

Bruce Montgomery, MD

Professor, Medical Oncology Division
University of Washington School of Medicine
(206) 598-0860
rbmontgo@uw.edu

Jonathan Wright, MD

Assistant Professor, Department of Urology
University of Washington School of Medicine
jlwright@uw.edu

Bladder Cancer Multispecialty Clinic

SCCA/UW Medicine's Bladder Cancer Multispecialty Clinic (BCMC) provides patients with consultation and input from the medical oncology, radiation oncology, and urologic oncology disciplines at once. The BCMC also includes same-day access to stoma nurses, physical therapy (pre-hab), and social work services.

Muscle-invasive bladder cancer requires specialized care, including careful coordination between providers and different treatment modalities. Although used for other tumors, multidisciplinary clinics for bladder cancer are rare. Multidisciplinary input on treatment recommendations or therapy coordination is a unique resource for patients and referring providers, which also serves as a platform for research and development of clinical trials.

BCMC operates as follows:

8:00 – 8:50 a.m.	History and physical with resident/fellow
9:00 – 9:50 a.m.	Case presentations and discussion » Review imaging and pathology with genitourinary radiologists and pathologists » Discuss comprehensive care plan
10:00 a.m. – 12:00 p.m.	Present plan to patient

To refer a patient to the BCMC, contact us at (206) 288-7222 or by fax at (206) 288-1025 or use our online referral form at www.seattlecca.org/referrals.

SEATTLE CANCER CARE ALLIANCE

Fred Hutchinson Cancer Research Center
UW Medicine
Seattle Children's

Seattle Cancer Care Alliance is a cancer treatment center that unites doctors from Fred Hutch, UW Medicine, and Seattle Children's. Our goal, every day, is to turn cancer patients into cancer survivors.

Seattle Cancer Care Alliance
825 Eastlake Ave. E.
P.O. Box 19023
Seattle, WA 98109-1023

(206) 288-SCCA (7222)
(800) 804-8824 Toll free
(206) 288-1025 Fax

www.seattlecca.org