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Seminar article

Bladder cancer clinical trials

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Abstract

The urologic oncology community recognizes the importance of bladder cancer as a significant public health problem. As the fourth most common malignancy diagnosed in U.S. men and the ninth most common in women, bladder cancer is a highly prevalent cancer with an estimated 5-year prevalence of 490,000 patients in the U.S. (2001) and over 1,000,000 worldwide (2004). Bladder cancer is the most expensive cancer to diagnose and treat. Important clinical questions abound and there are a growing number of both NIH and industry funded clinical trials attempting to answer these questions. The EORTC has played a critical role in conducting phase II and large phase III randomized trials addressing critical questions in the management of non-muscle invasive and invasive bladder cancer. The present article reviews this important area of clinical trials research.

Keywords: Bladder cancer; Clinical trials; Chemoprevention; Intravesical therapy; Chemotherapy; Immunotherapy

1. Introduction

There are many important questions being addressed in clinical trials for bladder cancer, ranging from detection and prevention to novel treatments strategies for both non-muscle invasive and invasive bladder cancer. Many institutions are investigating new chemotherapy agents, new combinations and sequencing of chemotherapy drugs, and the field of targeted therapy is emerging as an important area of research as well.

This review focuses on cooperative group and other multicenter trials that are recently completed, ongoing, or proposed with plans to open soon (Table 1). Please refer to individual cooperative group Web sites and the National Cancer Institute (NCI) Web site for other trials for additional information (Table 2). Several trials are open at Memorial Sloan Kettering and MD Anderson Cancer Centers, and information is available on their Web sites as well.

2. Detection

The field of voided urine biomarkers for detection of bladder cancer continues to develop. The Food and Drug Administration have now approved 2 cell-based assays for use as an adjunct to cystoscopy. The group at Johns Hopkins has revived the clinical testing of microsatellite polymorphism analysis. A new high-throughput assay has been developed by Cangen International (Irvine, CA) using 15 microsatellite markers, and this prospective clinical trial will determine the sensitivity and specificity for detection of bladder cancer compared to cystoscopy and cytology, and which of the markers are most predictive [1]. The study is enrolling 3 groups of patients: healthy controls (100), non-genitourinary cancer controls requiring cystoscopy (100), and new or recurrent Ta, T1 grade 1−3 transitional cell carcinoma (TCC) (300). Biomarkers will be obtained at baseline and every 3 months for 24 months. The study is the first in bladder cancer funded by the Early Detection Research Network and is being conducted at 11 sites in the United States. A multicenter trial of BLCA-4, which detects a bladder cancer specific nuclear matrix protein, is near completion, pending identification of a new sponsor.

PhotoCure ASA (Oslo, Norway) is sponsoring a follow-up US trial of 5-hexyl aminolevulinate (Hexvix®) and florescence cystoscopy for detection of occult papillary and carcinoma in situ (CIS) lesions. Studies conducted in Europe and results of the first US study were reported at the 2004 American Urological Association meeting. These results suggest that up to 26% of patients have occult papillary tumors, and the combination of standard and florescence cystoscopy detected 100% of CIS lesions, which if detected and eradicated, may lead to a lowering of the early and late recurrence rates. The current study was designed after ex-

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Table 1
High impact clinical trials in bladder cancer

Detection	Microsatellite polymorphism analysis	Johns Hopkins/EDRN
	BLCA-4	Multicenter
	5-hexyl aminolevulinate (Hexvix®)	PhotoCure ASA multicenter
Prevention	Fenretinide vs. placebo Ta G1,2	MDACC/NCI multicenter
	DFMO vs. placebo Ta, T1, G1,2	NCI/Ilex multicenter
	Celecoxib vs. placebo following BCG (6 + 3)	MDACC/NCI/Pfizer multicenter
	Green tea polyphenol vs. erlotinib	NCI/OSI Pharmaceuticals UCLA/ Mayo Clinic
Local	Perioperative single dose gemcitabine	SWOG 0337
	Gemcitabine for BCG refractory patients	SWOG 0353
	Full dose vs. 1/3 dose BCG and long vs. short-term maintenance BCG(Ta, T1)	EORTC 30962
	Sequential MMC/BCG + maintenance vs. Intravesical thermotherapy + MMC vs. BCG	EORTC 30993
	BCG + maintenance	
	BCG + interferon alpha 2b	O'Donnell/Schering
	BCG + maintenance vs. BCG/interferon	Lamm/Schering
	BCG vs. epirubicin + iFNα2b (T1G2,3)	Steffan Lund/Scandinavia
	Mycobacterial cell wall-DNA vs. BCG	Morales/Bioniche Life Sciences Inc.
Advanced salvage	Bladder salvage with neoadjuvant Carboplatin, gemcitabine, paclitaxel	SWOG 0219
	Bid XRT + CDDP/paclitaxcel - Bladder preservation or cystectomy	RTOG 99-06
	XRT/5-FU/CDDP vs. XRT/paclitaxel/CDDP + adjuvant CDDP/gemcitabine	RTOG 02-23
Advanced adjuvant	Phase III adjuvant M-VAC based on P53 status in organ-confined cancer	USC multi-center, SWOG, NCIC, Europe
	Phase III adjuvant chemotherapy for P3, P4N0 or any N1–3	EORTC 30994/NCIC/ACOSOG
	Phase III GC vs. dose dense Gemcitabine/doxorubicin followed by paclitaxel/CDDP	CALGB 90104/MSKCC/ECOG
Metastatic	Phase III GC vs. GCT	EORTC 30987 Intergroup
	Phase II gemcitabine/paclitaxel	SWOG 0028
	Phase II irinotecan	SWOG 0306
	Phase II depsipeptide	SWOG 0400
	Phase II gemcitabine/cisplatin/Iressa	CALGB 90102
	Ixabepilone phase II	ECOG 3800
	Pemetrexed/gemcitabine phase II	ECOG 4802
	Vinflunine phase III/phase II	Bristol-Meyers Squibb
	Herceptin + paclitaxel/carboplatin/gemcitabine	Hussein/University of Michigan

Abbreviations: C = cisplatin; CDDP = cisplatin; G = gemicitabine; T = paclitaxel.

tensive consultation with the Food and Drug Administration, and could lead to approval of this novel detection strategy.

3. Chemoprevention

Primary (i.e., prevention of first occurrence of bladder cancer in at-risk patients) and secondary (i.e., prevention of recurrence of bladder cancer) chemoprevention is a rapidly growing field in urology as we learn more about bladder carcinogenesis and new therapeutic targets are identified. The long latency of bladder cancer and identification of biomarkers associated with earlier events create opportunities to test early detection strategies and interventions designed to reduce the risk of developing new or recurrent cancers.

Two trials have been completed in patients with new or recurrent Ta or T1 grade 1–2 tumors. The MD Anderson Cancer Center led a NCI funded clinical trial comparing fenretinide (Imaginis Corp., Greenville, SC), a potent inducer of apoptosis with activity in breast cancer and oral premalignant lesions, versus placebo treatment for 12 months in patients with Ta grade 1 and 2 tumors. This study was eventually combined with the Southwest Oncology Group (SWOG) study of fenretinide with modulation of G-actin as the primary endpoint in patients treated with bacille Calmette-Guérin (BCG). The MD Anderson Cancer Center study also evaluated retinoic acid receptor-beta, deoxyribonucleic acid (DNA) ploidy, fluorescence in situ hy-