LOCALIZED CANCER BLADDER: PREDICTIVE VALUE OF THE G1-CHECK POINTS FOR RESPONSE TO ADJUVANT THERAPY

Thesis

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Last but not least, I would like to dedicate this work for my family for their continued help and support

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Abstract

Introduction: Muscle invasive bladder cancer is an aggressive tumor. Radical cystectomy is considered the standard treatment. However, many patients experience local and distant relapse. The biological behavior cannot be adequately predicted by histological criteria alone.

Aim of work: To evaluate the role of 6 cell cycle and apoptosis regulatory markers (cyclinD1, CDK4, bcl2, bax, p16, and p14) as predictive and prognostic makers in muscle invasive bladder cancer and their relation to the treatment received

Patients and methods: One hundred and twenty nine patients with muscle invasive bladder cancer were included, 68 patients underwent surgery alone and 61 patients underwent surgery and postoperative radiotherapy. Immuno-histochemistry and differential PCR were used to determine the expression level of CDK4, bcl2, and bax. p16 and p14 were evaluated for homozygous deletion and/or promoter methylation.

Results: For a median follow up of 20 months there was no significant difference between the 2 studied groups (surgery versus surgery and radiotherapy) in terms of disease free or overall survival. Tumor extension, positive lymph nodes, and aberrant expression of cyclin D1, CDK4, bcl2, Bax, p16, p14 were all independent prognostic factors for disease free survival with a p value of 0.006, 0.002, 0.001,< 0.0001, <0.0001, <0.0001, 0.0001 respectively . On the other hand, positive lymph nodes, and aberrant expression of bcl2, bax, p16, and p14 were independent prognostic factors for overall survival with a p value of 0.02 <0.001, <0.001, <0.001, and 0.001 respectively. In the surgery group, cyclin D1, CDK4, p16, and p14 were predictors of loco-regional failure, while bcl2, bax and p14 were predictors of distant metastases. In the surgery and radiotherapy group bcl2, p16 and p14 were predictors of loco-regional failure, while bcl2, bax and p14 were predictors of distant metastases.

Conclusion: Cell cycle regulators are good prognostic and predictive markers in muscle invasive bladder cancer. Post operative radiotherapy for muscle invasive bladder cancer cannot yet be considered in the routine practice and larger studies are still needed to properly evaluate its role taking the molecular profile of the disease in consideration as a risk factor for response to treatment.

KEY WORDES

Localized
Predictive
Response

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List of Abbreviations

AF: accelerated fractionation

ATM: ataxia telangiectasia mutated

ATR: (ATM and Rad 3-related),

BUB:budding uninhibited by benzimidazole

CDK : cyclin dependant kinase

CDK1; cyclin dependant kinase1

CDK2: cyclin dependant kinase2

CDK4: cyclin dependant kinase4

CDK6: cyclin dependant kinase6

CDKI:cyclin dependant kinase inhibitor

CF: conventional fractionation (CF),

CIS: carcinoma in situ

CISCA: cisplatin, cyclophosphamide, adriamycin

CM: cisplatin/methotrexate)

CMV: methotrexate , vinblastine , , cisplatin

CR:complete response (CR)

CT: computerized tomography

DD-MVAC: dactinomycin D, methotrexate , vinblastine , adriamycin , cisplatin

DFS: disease free survival

DNA: deoxy-ribonucleic acid

DSB: double-stranded DNA breaks (s)

Eau:European association of urology

EORTC: European Organisation for Research and Treatment of Cancer

ESMO: European society of medical oncology .

FasL: Fas ligand

FGFR3:Fibroblast growth factor receptor 3

GADPH: glyceraldehyde-3-phosphate dehydrogenase
GBM: glioblastoma multiformis

HZ: hazard ratio

ISUP: international society of urology pathology

IVU:intravenous urography

LRF: loco-regional failure

MAD:mitotic arrest deficient

MDACC:M.D. Anderson Cancer Center (MDACC)

MDCT:multidetector-row CT

MDF: multiple daily fractionation

Mo; month

MRC:Medical Research Council

MRI: magnetic resonance imaging

MRN:the multifunctional Mre11-Rad50-Nbs1

MSAD:maximum short axis diameter

MSKCC: Memorial Sloan-Kettering Cancer Center

MVAC: methotrexate , vinblastine , adriamycin , cisplatin

MVEC: methotrexate , vinblastine , epirubucin, cisplatin

NCCN: national cancer network

NCI: National cancer institute

NEMROCK: Kasr Al-Aini Center of Clinical Oncology & Nuclear Medicine

NO: nitrogen oxide

or GC: gemcitabine , cisplatin

OS: overall survival

PAH: polycyclic aromatic hydrocarbons

pCR: pathological complete remission

PFS: progression free survival

pRB :retinoblastoma protein

PSA:prostate-specific antigen

QOL: quality of life

RB: retinoblastoma

RT: radiation therapy

RTOG: Radiation Therapy Oncology Group

SCC: Squamous cell carcinoma

SWOG: south western oncology group

SWOG: Southwest Oncology Group (SWOG

TCC: Transitional cell carcinoma

TCI: twice-daily radiotherapy with paclitaxel and cisplatin chemotherapy induction

TNM: tumor –node -metastasis

TUR: transuretheral resection

TURB: transurethral resection of the bladder

US: ultrasound

WHO: world health organisation

Yr: year

8-OHdG: 8-hydroxydeoxyguanosine

INTRODUCTION

In Egypt, bladder cancer constitutes one of the most common malignancies reaching up to 30% of all cancers in the NCI registry. The majority of tumors present at advanced stage with deep infiltration of all muscle wall ***(Hussain et al 2003)***.

Literature review demonstrates that bladder cancer among Egyptian patients has a unique molecular finger print that differs from that reported in western countries with more genetic aberrations, some of them were not reported in the classic transitional cell bladder cancer of the western countries, such as loss of genetic material at chromosome 19, 15q, and 22q ***(Bahnassy et al 2003).*** Although molecular features of the Egyptian bladder cancer have been extensively studied, yet molecular changes associated with specific response to therapy are still in their beginning ***(Knowles MA 2001).*** The few available studies in this context show that alterations affecting the G1 check points and genes controlling apoptosis have prognostic significance and predictive values ***(Sharokh et al 2006).*** Although the potential clinical utility of p53 alterations has received most attention, some other markers have been mentioned in relation to overall survival and response to treatment including cyclin D1, ERBB2, EGFR, bcl2 and cyclin dependant kinase inhibitors p21, p27, p16 ***(Shiina et al 2002) .***

However, as single markers genetic alterations have insufficient predictive power to be applied in the management of individual patients and the use of a panel of markers seems to be a potential solution for this problem. Already this prediction has been confirmed by 3 studies which have shown that transitional cell carcinoma with inactivated p53 and Rb has a worse prognosis than tumors with alteration of either gene alone ***(Sunanda et al 2004).*** Similarly, an Egyptian study has shown that nm23-H1, EGFR and p53 could be used as prognostic biomarkers in muscle invasive bilharzial bladder cancer patients, and that in addition to the standard pathological prognostic factors, a combination of these markers (≥ 2) has synergistic effects in stratifying patients into variable risk groups. The higher is the number of altered biomarkers, the higher will be the risk of disease progression and death ***(Khaled et al 2009).***

As yet no studies have attempted a comprehensive assessment of the key proteins involved in the G1check point, which seems to be an interesting point of research among Egyptian bladder cancer patients in relation to the therapeutic outcome.

Treatment of muscle invasive bladder cancer remains a challenge. The poor prognosis is attributed to the presence of clinically undetectable micro-metastases at the time of diagnosis. Therefore, therapeutic end points should consider local control, elimination of potential micro-metastases and maintaining a good quality of life without compromising survival ***(Hussain et al 2001).***

Radical cystectomy alone provides a 5-year survival of about 80% in patients with T2 lesions and less than 50% in T3 tumors ***(Gschwend et al, 2002).***

In Egyptian reports, local recurrence after radical cystectomy accounts for 60%, while distant metastases accounts for 30%. The overall risk of distant metastases at 5 years has been estimated to be 23% ***(Awwad et al 2001).***

Radical cystectomy with lymphadenectomy alone cannot achieve satisfactory survival for patients with pT3, pT4 and node-positive disease. Those patients need additional treatments for improvement of their survival. Adjuvant and neoadjuvant chemotherapies have their own advantages and disadvantages ***(Tsukamoto et al 2004).***

Post operative radiotherapy has not been widely studied with only one randomized study ***(Zaghloul et al 1992)***, and few retrospective studies showing its benefit ***(Zaghloul et al 2002, Zaghloul et al 2006).***

Moreover, the role of molecular markers has been studied in bladder cancer patients receiving only radical cystectomy or with chemotherapy. However their predictive power was not studied in patients receiving post operative radiotherapy.