Actas Urol Esp. 2011;35(8):439–445

Actas Urológicas Españolas

www.elsevier.es/actasuro

ORIGINAL ARTICLE

Hexaminolevulinate photodynamic diagnosis in non-muscle invasive bladder cancer: Experience of the BLUE group☆

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Received 25 February 2011; accepted 11 March 2011

KEYWORDS
Photodynamic diagnosis;
Hexaminolevulinate;
Non-muscle invasive bladder cancer

Abstract
Objectives: Photodynamic diagnosis (PDD) with hexaminolevulinate has been recently used to improve detection of non-muscle invasive bladder cancer. Our main purpose was to quantify the benefit of PDD versus conventional white light cystoscopy (WL) in our area.
Materials and methods: Fluorescence-guided cystoscopy using hexaminolevulinate was performed at the time of the transurethral resection (TUR) in 305 patients from 7 Spanish hospitals. All lesions found with WL and PDD were numbered and recorded in an online database. Each lesion was sent separately for pathology analysis. Random biopsies were also obtained in 148 patients.
Results: A total of 1659 lesions were biopsied: 522 were identified with PDD and WL, 237 only with PDD, 19 only with WL and 881 random biopsies. Of the 600 tumors, PDD detected 563, WL 441 and random biopsies 29 (20 CIS). The mean overdetection rate for PDD over WL was 31.9% for all types of lesions, but it was 209% for carcinoma in situ (CIS). Sensitivity was 93.8% for PDD and 78.2% for WL. Specificity was 81.5% for PDD and 90.5% for WL. In 23% of patients, PDD detected at least one more neoplastic lesion than with WL.
Conclusions: Hexaminolevulinate fluorescence cystoscopy improves detection and resection of non-muscle invasive bladder cancer, especially of CIS. Sensitivity of PDD is higher than WL, but specificity is lower. In our study, random biopsies were able to detect some CIS not visible under PDD.

☆ Please cite this article as: Burgues JP, et al. Diagnóstico fotodinámico con hexaminolevulinato en el cancer vesical no músculo invasivo: experiencia del grupo BLUE. Actas Urol Esp. 2011;35:439–445.

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2173-5786/$ – see front matter

PALABRAS CLAVE
Diagnóstico fotodinámico;
Hexaminolevulinato;
Cáncer vesical no músculo invasivo

Diagnóstico fotodinámico con hexaminolevulinato en el cáncer vesical no músculo invasivo: experiencia del grupo BLUE

Resumen

Objetivos: El diagnóstico fotodinámico (DFD) con hexaminolevulinato se ha empezado a utilizar recientemente para mejorar la detección del cáncer vesical no músculo invasivo. Nuestro objetivo principal fue comparar el rendimiento diagnóstico de PDD frente a endoscopia con luz blanca convencional (LB) en nuestro medio.

Material y métodos: Se realizó cistoscopia fluorescente con hexaminolevulinato en el momento de la RTU a 305 pacientes de 7 hospitales españoles. Todas las lesiones detectadas con LB y DFD fueron enumeradas y registradas en una base de datos *online*. Se analizó histopatológicamente cada lesión por separado. En 148 pacientes se tomaron además biopsias múltiples aleatorias (BMA).

Resultados: Se biopsiaron un total de 1.659 lesiones: 522 identificadas con DFD y LB, 237 sólo con DFD, 19 sólo con LB y 881 BMA. De 600 neoplasias diagnosticadas DPD detectó 563, LB 441 y BMA 29 (20 CIS). La tasa media de sobredetección de DPD sobre LB fue del 31,9% globalmente, pero en el caso del CIS fue del 209%. La sensibilidad de DFD fue 93,8% y la de LB 78,2%. La especificidad de DFD fue 81,5% y la de LB 90,5%. En el 23% de los pacientes se detectó al menos una lesión neoplásica más con DFD que con LB.

Conclusión: La RTU con hexaminolevulinato mejora el rendimiento diagnóstico y la calidad de la resección del cáncer vesical superficial, especialmente del CIS. La mayor sensibilidad de DFD es a costa de una menor especificidad. En nuestro estudio BMA rescató algunos falsos negativos de DPD para detectar CIS.

Introduction

Non-muscle-invasive bladder cancer (NMIBC) represents around 80% of bladder tumors. It is estimated that the bladder tumor is the second most prevalent urological neoplasia in the western world, 139,500 new cases being diagnosed each year in Europe.[1,2] Its clinical course is characterized by the succession of relapses, which require the performance of multiple endoscopic actions with diagnostic and therapeutic aim. This makes the NMIBC one of the neoplastic processes that consumes the most economic and sanitary resources, both at a material and human level. The main goal of surgical treatment is the eradication of neoplastic tissue and obtaining of tissue material to determine the degree of infiltration into the bladder wall. Several studies have shown that the quality of endoscopic resection of the NMIBC varies depending on the center, the surgeon's experience, the size of the tumor, its multifocality, the visibility conditions, etc. This variability in the quality of the resection will determine a higher or lower rate of residual tumors, and a higher or lower false early relapse rate.[3] But, in addition to resection as complete as possible, it is necessary to confirm or not the existence of carcinoma in situ (CIS) or other flat lesions of uncertain malignant potential (dysplasias), which carry a high recurrence rate and a high risk of progression. The problem is that often these flat lesions are not visible with conventional cystoscopy.

In recent years, the use of photodynamic diagnosis (PDD) methods has spread, based on the use of photosensitizing agents, which instilled in the bladder are taken avidly by the neoplastic tissues. Once incised with a beam of blue light (280–440 nm), they emit a typical red fluorescence that evidences tumoral lesions that with conventional white light (WL) would not be visible. Since the mid-90s, 5-aminolevulinate (5-ALA) had been used as a photosensitizing agent, not very much spread in our area, but with extensive experience in the center of Europe.[4–6] In the last 4 years, derivative of 5-ALA has started to be used, hexyl ester 5-ALA or hexaminolevulinate (HAL), which has better pharmacodynamic characteristics, greater lipid solubility, and a higher intensity of the light signal than 5-ALA with an equal tissue concentration.[7] All this has meant that HAL is currently the agent of choice in photodynamic diagnosis of NMIBC, with a clear superiority in the detection of lesions compared with conventional white light.[8–14]

The main aim of this work is to determine in our area the diagnostic yield of photodynamic diagnosis (PDD) in non-muscle invasive bladder carcinoma, compared with conventional white light (WL). As secondary objectives, we intend to analyze the usefulness of PDD in the detection of CIS, as well as validate and compare the results with those of the published series.

Materials and methods

Patient recruitment

Between December 2006 and December 2009, 305 patients belonging to 7 different urology departments of different public hospitals in the Spanish health network were recruited: Son Llatzer Hospital, Son Dureta Hospital (currently Son Espases), Central Hospital of Asturias, Arnau de Vilanova Hospital, Marina Baixa Hospital, Valencian Institute of Oncology, and Royo Villanova Hospital. These centers belong to the BLUE (*Blue Light Urologic Endoscopy*) group,