REducing recurrence in non-muscle-invasive bladder cancer using photodynamic diagnosis and immediate post-transurethral resection of the bladder chemoprophylaxis

Malene Risager Lykke, Tommy Kjaergaard Nielsen, Nanna Andersen Ebbensgaard and Karsten Zieger

Hexvix® blue-light cystoscopy and immediate post-TURB chemoprophylaxis effectively reduce the risk of recurrence and the number of follow-up procedures in routine clinical practice

Hexvix®
Hexaminolevulinate 85mg

TURB: transurethral resection of the bladder
KEY FINDINGS

Introduction of Hexvix BLC and immediate post-TURB MMC into routine clinical practice*:

- Significantly reduced the risk of NMIBC recurrence by 41%
- Reduced the number of follow-up TURBs by one third
- Achieved savings of ~1,500 DKK (~€200) in first year of follow up

Click on bubbles for further information

Reductions in recurrence rates and the need for invasive monitoring are likely to be key contributors to improved quality of life for patients with NMIBC¹

*Compared with standard WLC and no immediate intravesical chemotherapy following TURB

BLC: blue-light cystoscopy; DKK: Danish Krone; MMC: mitomycin C; NMIBC: non-muscle-invasive bladder cancer; TURB: transurethral resection of the bladder; WLC: white-light cystoscopy
Patients therefore require frequent and regular follow up, making bladder cancer one of the most expensive cancers to manage\(^2\)–\(^3\)

Recurrence risk can be reduced using:
- Hexvix BLC, which improves tumor detection and resection vs WLC alone\(^4\)
- A single post-TURB instillation of chemotherapy (e.g. MMC)\(^5\)

THE PRESENT STUDY INVESTIGATED THE EFFECT OF HEXVIX BLC AND MMC INTRODUCED SIMULTANEOUSLY UNDER ROUTINE CLINICAL CONDITIONS

References
2006–2008: control group
Before BLC-TURB and MMC

- WLC-TURB with:
  - 6 routine selected-site biopsies for primary lesions
  - Selected-site biopsies at surgeon’s discretion for recurrent lesions (or routinely if cytology was positive)

2008–2010: intervention group
Following introduction of BLC-TURB and MMC

- Hexvix Instilled into bladder 1-4 hours before BLC-TURB
  - Biopsies of suspicious lesions (i.e. not preselected sites)
- Single-dose MMC instilled into bladder <24 hours post-TURB

- Similar use of BCG, second TURB, and referral for cystectomy between groups (click here for more information)

- Similar follow-up schedules between groups (click here for more information)
RESULTS

- Comparable baseline characteristics between groups

- Mean follow-up duration (cut-off February 2013):
  - Control: 36.3 months (range 0–82.5)
  - Intervention: 29.1 months (range 0–51.4)

Control: n=216

Intervention: n=190

• NB: ~50% not treated as planned, reflecting real-world clinical practice
41% REDUCTION IN RISK OF RECURRENCE WITH BLC-TURB + MMC

Intervention group vs control group:
HR 0.59 (95% CI 0.45–0.78)
p=0.0002

BLC: blue-light cystoscopy; CI: confidence interval; HR: hazard ratio;
MMC: mitomycin C; TURB: transurethral resection of the bladder

Click on pink and blue lines for more information
41% REDUCTION IN RISK OF RECURRENCE WITH BLC-TURB + MMC

Median recurrence-free survival:
- Control group: 13.6 months
- Intervention group: 36.8 months

Intervention group vs control group:
HR 0.59 (95% CI 0.45–0.78)
p=0.0002

BLC: blue-light cystoscopy; CI: confidence interval; HR: hazard ratio; MMC: mitomycin C; TURB: transurethral resection of the bladder
41% REDUCTION IN RISK OF RECURRENCE WITH BLC-TURB + MMC

Recurrence rate after 2 years’ follow up:
- Control group: 60%
- Intervention group: 38%
  - Absolute risk reduction 22%
  - Relative risk reduction 33%

BLC: blue-light cystoscopy; CI: confidence interval; HR: hazard ratio;
MMC: mitomycin C; TURB: transurethral resection of the bladder
ONE THIRD OF FOLLOW-UP TURBS AVOIDED WITH BLC TURB + MMC

FOLLOW-UP TURBS/PATIENT-YEAR

32% relative reduction in TURBs per patient-year of follow up with BLC TURB + MMC vs WLC TURB alone (P<0.0001)

BLC: blue-light cystoscopy; CIS: carcinoma in situ; MMC: mitomycin C; TURB: transurethral resection of the bladder; WLC: white-light cystoscopy
PATIENTS WITH LOW-RISK TUMORS (BOTH PRIMARY AND RECURRENT) BENEFITED MOST

Click on a subgroup for more information

**Stage** (Ta or CIS/T1)

**Tumor grade** (low/intermediate or high)

**Urine cytology**
(negative or positive)

**History**
(primary or recurrent)

CIS: carcinoma in situ
STAGE (Ta OR CIS/T1)

CIS: carcinoma in situ;
TURB: transurethral resection of the bladder
GRADE (LOW/INTERMEDIATE OR HIGH)

**RECURRENTS/PATIENT-YEAR**

- Control: 0.6, 1.2 (p<0.0001)
- Intervention: 0.3, 0.9 (p=0.13)

**FOLLOW-UP TURBS/PATIENT-YEAR**

- Control: 0.8, 1.6 (p<0.0001)
- Intervention: 0.4, 1.4 (p=0.25)

TURB: transurethral resection of the bladder
URINE CYTOLOGY (NEGATIVE OR POSITIVE)

**RECURRENTS/PATIENT-YEAR**

<table>
<thead>
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<th></th>
<th>Control</th>
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<tbody>
<tr>
<td>Negative</td>
<td>0.7</td>
<td>0.3</td>
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<tr>
<td>Positive</td>
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p<0.0001  p=0.87

**FOLLOW-UP TURBS/PATIENT-YEAR**

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<th>Control</th>
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<tr>
<td>Negative</td>
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<tr>
<td>Positive</td>
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p<0.0001  p=0.57

BLC: blue-light cystoscopy; CIS: carcinoma *in situ*; MMC: mitomycin C; TURB: transurethral resection of the bladder; WLC: white-light cystoscopy
HISTORY (PRIMARY OR RECURRENT)

RECURRENTS/PATIENT-YEAR

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<thead>
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<td>Primary</td>
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<td>0.5</td>
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<tr>
<td>Recurrent</td>
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<td>0.4</td>
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p=0.0002
p=0.004

FOLLOW-UP TURBS/PATIENT-YEAR

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<tr>
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<th>Control</th>
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<tr>
<td>Primary</td>
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<td>0.8</td>
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<tr>
<td>Recurrent</td>
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<td>0.7</td>
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p=0.0008
p=0.002

BLC: blue-light cystoscopy; MMC: mitomycin C; TURB: transurethral resection of the bladder
SAVINGS OF ~1,500 DKK (~€200) PER PATIENT IN FIRST YEAR OF FOLLOW UP

- Use of Hexvix BLC and MMC was cost effective in a Danish healthcare setting

<table>
<thead>
<tr>
<th>Additional costs/ patient vs WLC TURB alone</th>
<th>DKK*</th>
<th>APPROXIMATE € EQUIVALENT</th>
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<th>Cost savings/ patient vs WLC TURB alone in first year of follow up</th>
<th>DKK*</th>
<th>APPROXIMATE € EQUIVALENT</th>
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<tbody>
<tr>
<td>8,500</td>
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<td>1,135</td>
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</table>

*Based on Danish prices in 2008
†Does not include costs for saved check cystoscopies, patient discomfort, and lost working days
BLC-TURB + MMC WAS WELL TOLERATED

- Most adverse events seemed to be related to the tumor and TURB rather than to Hexvix or MMC, e.g.
  - Mild bladder pain
  - Bladder spasm
  - Dysuria
  - Mild hematuria
CLINICAL RELEVANCE

• In routine clinical practice, BLC-TURB + MMC reduce the risk of recurrence and the need for follow-up procedures vs standard WLC-TURB offering:

  Longer recurrence-free survival

  Less burden on patients from repeated TURB

  Reduced pressure on healthcare resources

• Real-world studies such as this are important to confirm and validate the benefits of Hexvix BLC and MMC in patients with NMIBC seen in clinical trials (click here for more information)
PRESCRIBING INFORMATION: HEXVIX® (HEXAMINOLEVULINATE)

Please refer to full national Summary of Product Characteristics (SPC) before prescribing. Indications and approvals may vary in different countries. Further information available on request. Hexvix 85 mg, powder and solvent for solution for intravesical use.

PRESENTATION Pack of one 10ml glass vial containing 85mg of hexaminolevulinate as 100mg hexaminolevulinate hydrochloride as a powder and one 50ml polypropylene vial containing solvent. After reconstitution in 50ml of solvent, 1ml of the solution contains 1.7mg hexaminolevulinate which corresponds to a 8mmol/l solution of hexaminolevulinate.

INDICATIONS This medicinal product is for diagnostic use only. Hexvix blue light fluorescence cystoscopy is indicated as adjunct to standard white light cystoscopy to contribute to the diagnosis and management of bladder cancer in patients with known or high suspicion of bladder cancer.

DOSAGE AND METHOD OF ADMINISTRATION Hexvix cystoscopy should only be performed by health care professionals trained specifically in Hexvix cystoscopy. The bladder should be drained before the instillation. Adults (including the elderly): 50 ml of 8 mmol/l reconstituted solution (see section 6.6) is instilled into the bladder through a catheter. The patient should retain the fluid for approximately 60 minutes. Following evacuation of the bladder, the cystoscopic examination in blue light should start within approximately 60 minutes. The cystoscopic examination should not be performed more than 3 hours after Hexvix is instilled in the bladder. Also if the retention time in the bladder is considerably shorter than one hour, examination should start no earlier than after 60 minutes. No minimum retention time has been identified making examination non-informative. For optimal visualization it is recommended to examine and map the entire bladder under both white and blue light before any surgical measures are initiated. Biopsies of all mapped lesions should normally be taken under white light and complete resection should be verified by switching to blue light. Only CE marked cystoscopic equipment should be used, equipped with necessary filters to allow both standard white light cystoscopy and blue light (wavelength 380–450 nm) fluorescence cystoscopy. Children and adolescents: There is no experience of treating patients below the age of 18 years.

CONTRAINDICATIONS Hypersensitivity to the active substance or to any of the excipients of the solvent. Porphyria.

WARNINGS AND PRECAUTIONS The possibility of hypersensitivity including serious anaphylactic/anaphylactoid reactions should always be considered. Advanced life support facilities should be readily available. Repeated use of Hexvix as part of follow-up in patients with bladder cancer has not been studied. Hexaminolevulinate should not be used in patients at high risk of bladder inflammation, e.g. after BCG therapy, or in moderate to severe leucocyturia. Widespread inflammation of the bladder should be excluded by cystoscopy before the product is administered. Inflammation may lead to increased porphyrin build up and increased risk of local toxicity upon illumination, and false fluorescence. If a wide-spread inflammation in the bladder becomes evident during white light inspection, the blue light inspection should be avoided. There is an increased risk of false fluorescence in the resection area in patients who recently have undergone surgical procedures of the bladder.

INTERACTIONS No specific interaction studies have been performed with hexaminolevulinate.

FERTILITY, PREGNANCY AND LACTATION No clinical data on exposed pregnancies are available Animal studies do not indicate direct or indirect harmful effects with respect to the reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of Hexvix during pregnancy.

UNDESIRABLE EFFECTS Most of the reported adverse reactions from clinical studies were transient and mild or moderate in intensity. The most frequently reported adverse reactions from clinical studies were bladder spasm, reported by 2.4 % of the patients, dysuria by 1.8%, bladder pain by 1.7 % and hematuria by 1.7%, of the patients. Other commonly reported adverse reactions are: headache, nausea, vomiting, constipation, diarrhea, urinary retention, haematuria, pyrexia and post procedural pain. Uncommonly reported adverse reactions are cystitis, sepsis, urinary tract infection, insomnia, urethral pain, pollakuria, micturition urgency, urinary tract disorder, back pain, incontinence, white blood cell count increase, bilirubin and hepatic enzyme increase, post operative fever, anemia, gout, rash and balanitis. The adverse reactions that were observed were expected, based on previous experience with standard cystoscopy and transurethral resection of the bladder (TURB) procedures.

OVERDOSE No case of overdose has been reported. No adverse events have been reported with prolonged instillation times exceeding 180 minutes (3 times the recommended instillation time), in one case 343 minutes. No adverse events have been reported in the dose-finding studies using twice the recommended concentration of hexaminolevulinate. There is no experience of higher light intensity than recommended or prolonged light exposure.

INSTRUCTIONS FOR USE AND HANDLING Hexaminolevulinate may cause sensitization by skin contact. The product should be reconstituted under aseptic conditions using sterile equipment.

MARKETING AUTHORIZATION HOLDER: Photocure ASA, Hofsvieen 4, N-0275 Oslo, Norway

PRICE Denmark DKK 4 718.50 Finland EUR 464.20 Norway NOK 4 234.50

Sweden SEK 4 222,00

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