TREATMENT CHANGES AND LONG-TERM RECURRENCE RATES AFTER HEXAMINOLEVULINATE (HEXVIX®) FLUORESCENCE CYSTOSCOPY: DOES IT REALLY MAKE A DIFFERENCE IN PATIENTS WITH NON-MUSCLE-INVASIVE BLADDER CANCER (NMIBC)?

Authors:
B Geavlete, R Multescu, D Georgescu, M Jecu, F Stanescu, P Geavlete

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AIM

To assess the impact of hexaminolevulinate (Hexvix®) blue-light cystoscopy versus standard white light cystoscopy alone on:

- The diagnosis of non-muscle-invasive bladder cancer (NMIBC).
- Changes in post-operative patient management.
- Long-term recurrence rates.

METHODS

- This trial was a single-center, prospective, randomized trial.
- Eligible patients had positive urine cytology and/or ultrasonographic suspicion of bladder cancer and underwent transurethral resection of their bladder tumor(s) (TURBT).
- Patients were randomized to one of two groups by means of sealed envelopes:
  - White light group (n=181).
    - Standard white light cystoscopy alone and TURBT.
  - Hexvix® group (n=181).
    - White light examination followed by conventional TURBT, then a Hexvix® blue-light examination followed by a Hexvix®-guided TURBT.
- Separate bladder maps of the lesions identified were developed during the white and blue-light cystoscopies.
- The urologist was informed whether Hexvix® blue-light cystoscopy could be performed only after finishing the white light procedure.
- All patients who underwent TURBT received a single shot of mytomycin C within 6 hours of surgery; patients were then managed dependent on their disease stage according to the European Association of Urology guidelines.
- All resected specimens were subject to central pathology review.
- The recurrence and progression risk of each patient was determined according to the European Organization for Research and Treatment of Cancer (EORTC) guidelines.
  - Follow-up protocol: urine cytology and white light cystoscopy every 3 months for 2 years.

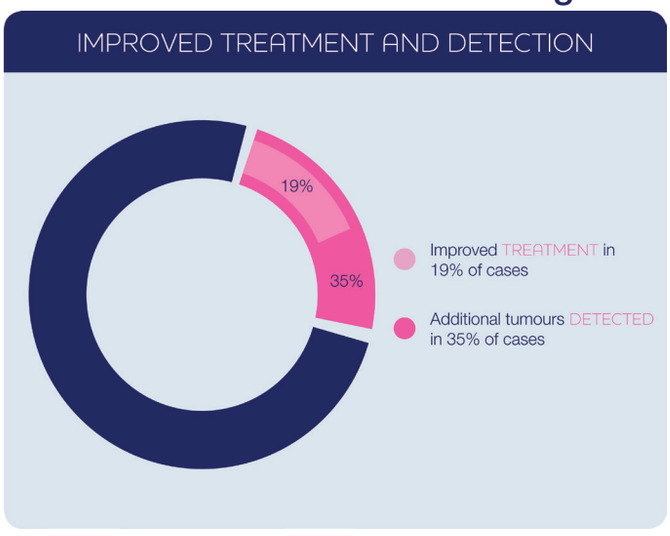
RESULTS

362 patients were randomized (n=181 to each arm).

Diagnosis of NMIBC

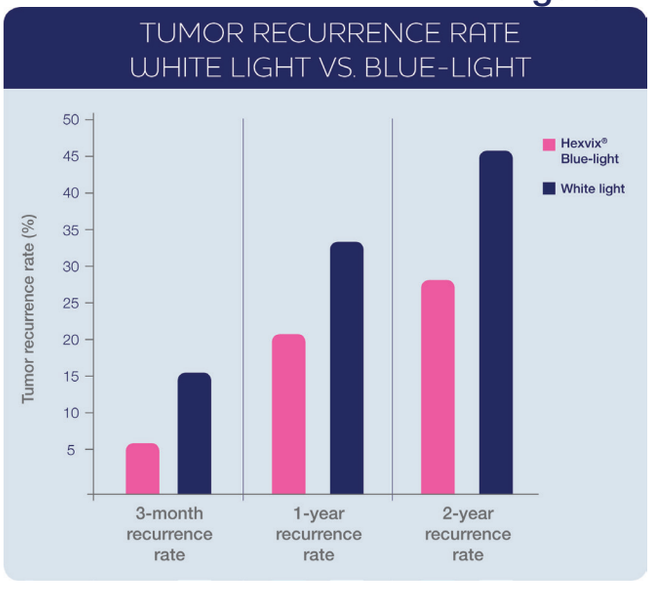
- The proportion of patients diagnosed with NMIBC was significantly higher with Hexvix® blue-light cystoscopy than with white light cystoscopy alone: 79% versus 70%; p=0.046.
- For the 142 patients in the Hexvix® group diagnosed with NMIBC, tumor detection rates were improved across all tumor stages (overall, CIS, pTa and pT1), though not significantly so for pT1 tumors.

Figure 1.



Hexvix® blue-light cystoscopy led to significant changes in post-operative patient management

Figure 2.



Changes in post-operative patient management

- In 35% of cases, additional tumors were detected with Hexvix® blue-light cystoscopy, resulting in amendments to the recurrence and progression risk categories to which the patients were originally assigned; treatment was more appropriate in 19% of these cases (see Figure 1).

Long-term recurrence rates

- 125 patients in the Hexvix® group and 114 patients in the white light group completed follow-up.
- Recurrence rates were significantly lower in the Hexvix® group than in the white light group at all time-points (see Figure 2) and for both initial and recurrent NMIBC.
- The progression rates did not differ statistically between groups:
  - At 1 year: Hexvix® group 2% versus white light group 4%.
  - At 2 years: Hexvix® group 4% versus white light group 7%.

CONCLUSION

Compared to white light cystoscopy, Hexvix® blue-light cystoscopy improves tumor detection rates and results in reduced recurrence rates at 3 months, 1 year and 2 years post diagnosis. Hexvix® blue-light cystoscopy also has a significant effect on post-operative treatment of patients.

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 considerable 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 visualisation 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, anaemia, 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 sensitisation by skin contact. The product should be reconstituted under aseptic conditions using sterile equipment.

MARKETING AUTHORISATION HOLDER
Photocure ASA, Hoffsveien 4, N-0275 Oslo, Norway

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