FLUORESCENCE GUIDED TRANS-URETHRAL RESECTION OF THE BLADDER REDUCES BLADDER TUMOR RECURRENCE DUE TO LESS RESIDUAL TUMOR TISSUE IN TA/ T1 PATIENTS: A RANDOMIZED 2-CENTER STUDY

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AIM

- To compare 12-month tumor recurrence rates after conventional white light transurethral resection of the bladder (TURB) and blue-light TURB, using hexaminolevulinate (Hexvix®) for photodynamic diagnosis (PDD).
- Secondary objectives were to relate the tumor recurrence rate to Hexvix® detected residual tumor after white light TURB, and to assess the rate of false positives.

METHODS

- This trial was a prospective, comparative, randomized, open-label study.
- Eligible patients were aged 18 years or older, had suspected Ta/T1 bladder tumors and were being treated at one of two Danish hospital outpatient departments.
- Eligible patients all received a Hexvix® instillation and were randomized to one of two treatment groups:
  - White light group: Patients in this group underwent cystoscopy and mapping of bladder lesions, followed by TURB with white light.
  - Hexvix® group: Patients in this group underwent cystoscopy and mapping of bladder lesions, followed by TURB in white light. After suspicious lesions and tumors had been mapped and biopsied and all identified lesions resected, the bladder was inspected again using Hexvix® blue-light cystoscopy to identify residual tumor tissue at the resection sites or additional tumors that had been missed with white light. Fluorescing lesions were recorded, biopsied and resected.
- Patients with macroscopic and histologically-confirmed Ta or T1 tumors were monitored for 4, 8 and12 months or until recurrence with flexible white light cystoscopy.

RESULTS

Of the 233 patients enrolled with suspected superficial bladder tumors, 115 were randomized to the Hexvix® group and 118 to the white light group.

Tumor Recurrence

- 145 patients (68 Hexvix® group; 77 white light group) were eligible for analysis of tumor recurrence.
- The recurrence-free period was significantly longer in the Hexvix® group than in the white light group (p=0.02; Figure 1).
- 12-month recurrence rate was 30.5% (18/59) after Hexvix® TURB and 47.3% (35/74) after white light TURB (p=0.05).
- 12-month relative and absolute reductions in recurrence rate for Hexvix® TURB were 35.5% and 16.8%, respectively.

Residual tumor detection

- 102 patients assessed with Hexvix® blue-light were eligible for the analysis of residual tumor detection.

- Hexvix® blue-light cystoscopy after white light TURB identified residual tumor tissue in 44/90 patients (49%).
- Figure 2 shows the number of patients with 1, 2, 3, >3 additional lesions seen with Hexvix® blue-light.

Rates of false positives

- On a lesion level, the false positive rates were 55% for Hexvix® TURB and 32% for white light TURB.

Figure 1

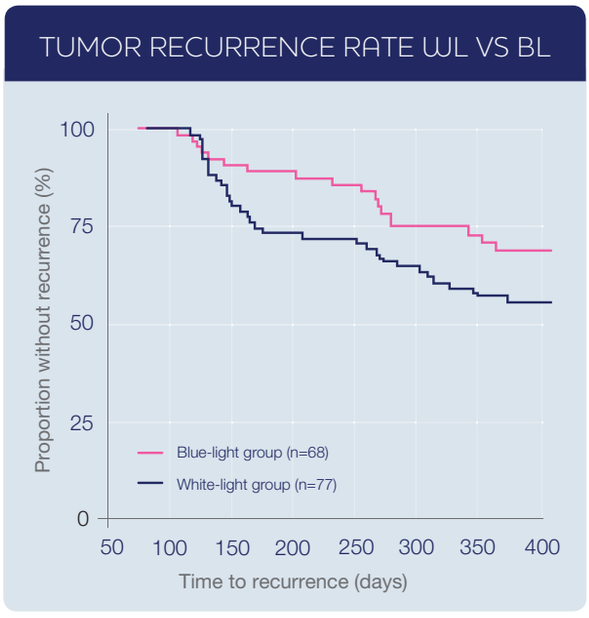
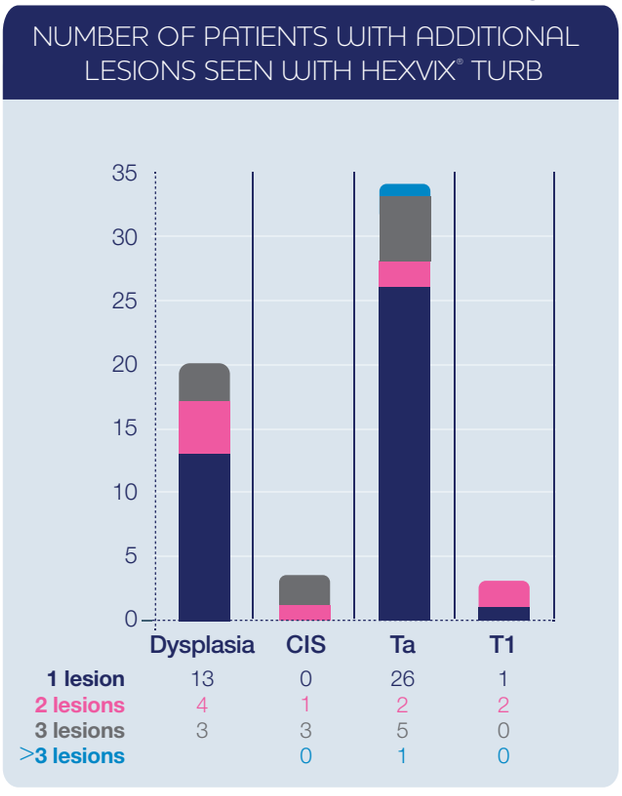


Figure 2



A large number of residual lesions were identified with Hexvix® blue-light TURB following a white light TURB.

CONCLUSION

White light TURB often leaves residual tumor in the bladder. Hexvix® blue-light TURB, when used in conjunction with white light, improves the detection of Ta/T1 tumors of the bladder, resulting in more complete TURB and thus a reduced recurrence rate at 12 months.

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
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