PHOTODYNAMIC DIAGNOSIS OF NON-MUSCLE INVASIVE BLADDER CANCER WITH HEXAMINOLEVULINATE CYSTOSCOPY: A META-ANALYSIS OF DETECTION AND RECURRENCE BASED ON RAW DATA

Authors:

Citation:
To analyze available clinical data (raw data from original studies) on hexaminolevulinate (Hexvix®) blue-light cystoscopy (BLC) in non-muscle invasive bladder cancer (NMIBC)

- On the effect of Hexvix BLC on the detection of Ta/T1 tumors and carcinoma in situ (CIS)
- On the impact of Hexvix BLC on tumor recurrence

Search of PubMed and the Cochrane Library for controlled trials of Hexvix BLC
- Search undertaken in July 2011
- A study was considered eligible if it met all of the following criteria:
  - Prospective trial enrolling consecutive patients meeting predefined inclusion criteria
  - Patients with known or suspected NMIBC (Ta, T1 or CIS) diagnosed by cystoscopy or positive urine cytology, or indicated by medical history
  - Compared single applications of Hexvix BLC and white light cystoscopy (WLC)
    - Either within-patient (detection) or randomized between-group comparison (recurrence)
  - Detection reported by lesion type (Ta, T1 and CIS) separately for BLC and WLC
  - Hexvix BLC carried out according to the recommended instructions
  - Used histology to confirm the nature of lesion (true or false)
  - Raw data available from study sponsor (Photocure) or investigators

Statistical analytical methods
- SAS v.9 was used to calculate endpoints, and the results were analyzed using Comprehensive Meta-Analysis software v.2.2
- Meta-analyses were performed using the random-effects model of DerSimonian and Laird to obtain pooled relative risks and associated 95% confidence intervals (CIs) for outcomes for detection
  - This model explicitly accounts for any heterogeneity of studies, and it coincides with the inverse variance fixed-effects method if there is no heterogeneity
- The fixed-effects model was used for recurrence analysis

Defined endpoints
- Detection
  - This endpoint was used to assess whether addition of Hexvix BLC to WLC improved detection of Ta/T1 tumors and CIS, at a lesion level (i.e. number of additional lesions detected) and patient level (i.e. number of patients in whom additional lesions were detected)
- Recurrence
  - This endpoint was used to assess whether improved tumor detection reduced the recurrence rate up to 12 months
• Subanalyses based on patient subgroups with different risk profiles:
  • Primary versus recurrent bladder cancer
  • Ta/T1 or CIS
  • Patients at high, intermediate or low risk of recurrence (high=any Ta G3, T1 or CIS; intermediate=multiple Ta G1 or Ta G2; low=single Ta G1 or Ta G2)

Of note: this meta-analysis used raw data from the trials meeting the eligibility criteria, rather than the published analyses (as a result, data reported in the meta-analysis may not match published reports). This method improves statistical accuracy and gives a more accurate picture of the potential benefit from Hexvix BLC, compared with individual study reports.

RESULTS

• The searches identified nine eligible studies involving 2,212 patients:
  • Eight studies (1345 patients) were available for detection analysis
  • Three studies (634 patients) assessed recurrence up to 12 months
• Raw data on detection/recurrence outcomes and some baseline characteristics (age, sex, primary/recurrent bladder cancer, previous treatments and risk status) were collected from the following sources:
  • Photocure database (for data from six studies, including the five registration trials1–7)
  • Directly from investigators

Detection

• Hexvix BLC detected a significant proportion of NMIBC lesions that were not seen under WLC:
  • Ta tumors: 14.7% (p<0.001; odds ratio [OR] 4.898, 95% CI 1.937–12.390)
  • T1 tumors: 10.8% (p=0.050; OR 2.253, 95% CI 0.999–5.081)
  • CIS lesions: 40.8% (p<0.001; OR 12.372, 95% CI 6.343–24.133)

Of note: while detection of any T1 tumor reached only borderline significance (p=0.050), detection of primary T1 lesions was highly significantly increased with Hexvix BLC (p=0.001). There were fewer T1 tumors in total in the combined studies (n=372) compared with Ta (n=1621) and CIS (n=527).

• ≥1 additional Ta/T1 tumor was seen with Hexvix BLC compared with WLC in a significant proportion of patients (meta-analysis event rate):
  • Overall: 24.9% (p<0.001)
  • Patients with primary tumors: 20.7% (p<0.001)
  • Patients with recurrent tumors: 27.7% (p<0.001)
  • Patients at high risk: 27.0% (p<0.001)
  • Patients at intermediate risk: 35.7% (p=0.004)
  • Patients at low risk: 5.4% (p<0.001)
• CIS was detected by Hexvix BLC only in a significant proportion of patients (meta-analysis event rate):
  • Overall: 26.7% (p<0.001)
  • Patients with primary tumors: 28.0% (p<0.001)
  • Patients with recurrent tumors: 25.0% (p<0.001)

   Previous intravesical therapy had no effect on tumor detection

**Recurrence**

- Recurrence rates up to 12 months were significantly lower with Hexvix BLC than with WLC:
  - Overall: 34.5% vs 45.4% (p=0.006; risk ratio [RR] 0.761, 95% CI 0.627–0.924)
  - Patients with T1 or CIS tumors: 35.1% vs 51.7% (p=0.052; RR 0.696, 95% CI 0.482–1.003)
  - Patients with Ta tumors: 35.9% vs 44.4% (p=0.040; RR 0.804, 95% CI 0.653–0.991)
  - Patients at high risk: 36.5% vs 48.6% (p=0.05; RR 0.752, 95% CI 0.565–1.000)
  - Patients at intermediate risk: 45.3% vs 54.1% (p=0.246; RR 0.836, 95% CI 0.617–1.132)
  - Patients at low risk: 17.9% vs 34.7% (p=0.029; RR 0.561, 95% CI 0.334–0.944)

**Of note:** the meta-analysis showed an overall reduction in recurrence at 12 months of approximately 11% (p=0.006; RR 0.761, 95% CI 0.63–0.92). In patients with CIS or T1, the decrease in recurrence rate was 16.6% (p=0.052; RR 0.696, 95% CI 0.48–1.003).
No conclusions could be drawn about time to recurrence or disease progression because:

- The three studies reporting recurrence presented contradictory results about time to recurrence
- The follow-up duration in these studies (12 months) is insufficient to detect progression to invasive cancer

Note:
- Extended follow up of one of the studies included in the meta-analysis (Stenzl A, et al. J Urol 2010;184:1907–13), which was published after the search in this meta-analysis, showed that the time to recurrence was significantly better in the Hexvix BLC group compared to WLC group with a trend toward improved bladder preservation
- There was also a trend toward a lower rate of cystectomy, which was possibly an indirect indicator of lower disease progression

**CONCLUSION**

- A single application of Hexvix BLC detects significantly more NMIBC lesions than WLC alone
  - Benefit is particularly high in patients with CIS, whose cancer may not be detected with WLC alone
  - Benefit is seen in both primary and recurrent cancer and in all risk groups
  - Improved detection with Hexvix BLC is associated with significantly reduced recurrence rates up to 12 months
  - Reduced recurrence risk might translate into less frequent need for resection

**Research published since this meta-analysis**

- Recent studies published after the literature search for this meta-analysis support the above conclusions:
  - Lapini et al reported improved detection of tumors and significantly greater sensitivity with Hexvix BLC compared with WLC
  - Karaolides et al reported recurrence-free survival of 91% at 12 months and 82.5% at 18 months in patients undergoing Hexvix BLC compared with 56.3% and 50.6%, respectively, in patients having WLC only
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 widespread 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, pollakiuria, micturition urgency, 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

PRICE Denmark DKK 4 718.50 Finland EUR 464.20 Norway NOK 4 234.50 Sweden SEK 4 222.00

DATE OF REVISION OF TEXT February 2013.

Hexvix is a registered trademark of Photocure ASA