Safety of Hexaminolevulinate for Blue Light Cystoscopy in Bladder Cancer. A Combined Analysis of the Trials Used for Registration and Postmarketing Data

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OBJECTIVE To detail and put into perspective, safety of hexaminolevulinate blue light cystoscopy (HAL-BLC), including repeated use, based on combined data of controlled trials used for registration of HAL and postmarketing experience.

METHODS Safety data of 2 randomized comparative studies (group 1) and 4 within patient control studies (group 2) were combined. Postmarketing data from >200,000 patients were analyzed.

RESULTS In group 1, 533 patients were examined with HAL-BLC and 499 with white light (WL) cystoscopy. In group 2, 791 patients were examined with both WL and HAL-BLC. Between 73% and 93% of these patients had concomitant diseases. Between 41% and 58% of the patients had at least 1 adverse event (AE), although predominantly mild to moderate. The majority was considered as not related to HAL-BLC and reported in the urinary tract. No serious adverse events (SAEs) were considered definitely related to HAL-BLC, but in 6 patients serious AEs were of an uncertain relationship. Four possibly related hypersensitivity reactions have been reported. Repeated use did not reveal additional toxicity, also supported by data from 3 European centers.

CONCLUSION This combined and detailed analysis of patients from 6 HAL-BLC studies with very comparable criteria shows that HAL-BLC is safe and poses very little additional risks other than expected for WL cystoscopy for bladder tumor resection in this specific patient population. This is supported by 9 years of postmarketing experience. Repeated use also seems safe. UROLOGY 84: 122–126, 2014. © 2014 Elsevier Inc.

There have been only few new developments in the diagnosis and treatment of bladder cancer in recent decades. For example, in the treatment of non–muscle-invasive bladder cancer (NMIBC), Bacille Calmette-Guérin was registered in the mid eighties. If therapy was very effective, this would not be a major issue. However, recurrence rates in NMIBC are as high as 80% in high-risk patients after some years, thus creating an urgency to improve management.[1]

In the last decade, blue light cystoscopy (BLC) has become the standard of practice in many centers, although it is not yet uniformly recommended by guidelines. BLC is done with hexaminolevulinate (HAL), which has been registered for this indication. HAL-BLC has proven to detect more bladder tumors, enabling a better tumor resection and better patient management. These effects result in a lower short-term and long-term recurrence rates of NMIBC.[2-10] A recent systemic review showed that 20% more patients with papillary tumors were detected, and 39% more carcinoma in situ (CIS) patients.[2] This resulted in less residual tumor (odds ratio, 0.28) and a higher recurrence-free survival ($P = .00002$). Based on the reduction in long-term recurrence rate,[10] the registered indication of this drug changed from a pure detection tool to a drug that improves diagnosis and management of patients with blood cancer. The European Association of Urology guideline recommends BLC in certain cases of (suspected) NMIBC.[11] In all, the effectiveness of HAL-BLC is clearly proven.

Safety of HAL-BLC has been registered in all studies, and BLC with HAL is considered safe and well tolerated. Some of these data have also been reported in the

Financial Disclosure: *J. Alfred Witjes is a paid consultant to Ipsen and Photocure; Arnulf Stenzl is a paid consultant to Photocure, Ipsen, and Storz; Sam Chang is a paid consultant to Photocure and Endo Pharm; Dirk Zaak is a paid consultant to Photocure, GE Healthcare, and Ipsen; and Leonard Gomella and H. Barton Grossman are paid consultants to Photocure.*

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Submitted: January 7, 2014, accepted (with revisions): March 4, 2014

0090-4295/14/$36.00
http://dx.doi.org/10.1016/j.urology.2014.03.006

publications of these studies.[3-9] The aim of this study was to show a favorable safety profile of HAL-BLC, which could well be an additional reason to embrace on this new technique, of which improved effectiveness is proven. The second aim was to report on the safety of repeated use of HAL, which is not in the labeling of HAL in the US, and for which no prospective information is available, but what is expected and done because of the recurrent nature of the disease.

This safety summary provides a review of detailed safety data collected in 6 controlled clinical trials conducted with HAL powder for solution, which were the basis for the Food and Drug Administration approval 2010. Information from postmarketing experience is also presented.

PATIENTS AND METHODS

Six controlled studies were used for this safety analyses and review. Details and results of these studies have been published before.[3-9] For all centers in these 6 studies, ethics committee approval was obtained and for all patients informed consent was obtained. Patient selection and treatment is very similar in all the 6 studies. All the studies used a single dose HAL 8-mM solution. Cystoscopy was done with the Karl Storz PDD D-light System. In all studies, patients had a resection of papillary tumors or biopsies of suspicious areas seen during white light (WL) or BLC.

Four studies were within patient control studies (B201/00, B301/01, B302/01, and B303/01); in these studies, all patients had HAL-BLC as well as WL cystoscopy. Studies B304/04 and B305/04 were randomized comparative studies, where patients were randomized to have the inspection and transurethral resection of a tumor (TURB) with WL or HAL-BLC after WL.

Because the 6 controlled clinical studies were very comparable, safety data were combined to study the safety profile of HAL-BLC in detail in this patient population. Adverse event (AE) definitions and description of baseline voiding were the same throughout the 6 studies. Safety evaluations performed per study were registration of AEs and concomitant medications in all 6 studies; hematology and biochemistry were additionally registered in studies B201/00, B301/01, and B302/01; vital signs and physical examination were registered in studies B301/01, B302/01, B303/01, and B305/04. AEs were assessed from the time of HAL instillation until exit from the study. Treatment-emergent AEs were defined as those events that occurred or worsened after exposure had begun. For patients in studies B305/04 and B304/04, who were randomized to the standard cystoscopy arms, treatment-emergent AEs were events that occurred or worsened after the initiation of the standard cystoscopy procedure. AEs considered by the investigator to be related to HAL-BLC with a high degree of certainty or AEs where a relationship to HAL-BLC could not be ruled out are presented together as "related AEs." In the 305 extension study, 39 of 551 participants (both in the BLC and in the WL group) had multiple HAL instillations after the initial study period. Data on possible anaphylactic reactions with repeated use were collected retrospectively. The postmarketing data were obtained from reporters (eg, urologists, pharmacist, and even patients) to Photocure and its licensed partner. All reports, both serious and nonserious case reports, are entered into a global safety database. This is a standard method for collecting of AEs postmarketing, following international regulations (The European Union and United States). All case reports (CIOMS I) included in the global database were retrieved and analyzed for this publication.

Table 1. Bladder symptoms at study entry in the safety set, when recorded

Bladder Symptoms	Group 1 HAL (n = 533), n (%)	Group 1 WL (n = 499), n (%)	Group 2 HAL (n = 791), n (%)
Hematuria			
Yes	48 (9.0)	34 (6.8)	134 (16.9)
No	372 (69.8)	346 (69.3)	655 (82.8)
Missing	0 (0.0)	0 (0.0)	2 (0.3)
Painful urination			
Yes	21 (3.9)	17 (3.4)	60 (7.6)
No	399 (74.9)	363 (72.7)	729 (92.2)
Missing	0 (0.0)	0 (0.0)	2 (0.3)
Frequent urination or the urge to urinate, but without results			
Yes	45 (8.4)	46 (9.2)	158 (20.0)
No	374 (70.2)	334 (66.9)	631 (79.8)
Missing	1 (0.2)	0 (0.0)	2 (0.3)

HAL, hexaminolevulinate; WL, white light.

RESULTS

Efficacy

As mentioned previously, results of these 6 studies have been published before.[3-9] In short, all 6 studies showed significant increased detection rate with HAL-BLC, especially for CIS. Two studies also looked at recurrence rate as end point. Both studies showed an advantage for patients treated with HAL-BLC.[3,4]

Safety

The studies combined for the safety analysis have been grouped as follows: in group 1, patients are included who received HAL-BLC (n = 533 and median age of 69.0) or WL (n = 499 and median age of 69.5) cystoscopy in studies B305/04 and B304/04; in group 2, 791 patients (median age of 68.5) are included from the 4 older studies (B201/00, B301/01, B302/01, B303/01), in which patients had HAL-BLC after WL cystoscopy during the same procedure and anesthesia. The male-to-female ratio was 3.2:1. Although majority of the patients had recurrent tumors, most had not received intravesical therapy before.

As expected in a group of older patients with bladder cancer, multiple comorbidities and concomitant medications were noted in 86.8% (HAL group 1), 73.3% (WL group 1), and 93% (group 2) of patients. Baseline bladder symptoms, noted and registered at study entry, are shown in Table 1. Data from individual studies were pooled to create integrated data sets for each of the data domains.

In Table 2, the number of AEs and serious adverse events (SAEs) is listed, their relation to HAL, treatment discontinuation, and deaths occurring during the study period. AEs per body system are detailed per degree of severity in Table 3 (HAL-BLC vs WL in group 1) and Table 4 (group 2). As expected, the most frequently involved body system in patients treated for bladder