Observational Studies Requested by European Health Authorities: Governmental Interference or an Enhancement of Everyday Urological Practice? The Hexvix® Observational Patients Evaluation Study as an Example of What to Expect

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Keywords

European Union regulation · Observational studies · Hexaminolevulinate · Non-muscle invasive bladder cancer

Abstract

Objective: The Hexvix® Observational Patients Evaluation (HOPE) study was designed to determine the extent of distribution of the use of hexaminolevulinate in the diagnosis of non-muscle invasive bladder cancer (NMIBC) and assess patient and treatment characteristics associated with different endoscopic modalities and to address the French authorities' request for information on routine practices for NMIBC diagnosis and surveillance. **Patients and Methods:** A prospective, observational study in 30 centres in France with fluorescence endoscopy equipment available. All candidates for endoscopy with transurethral resection who gave their consent were eligible. The primary endpoint was the proportion of patients with an NMIBC diagnosis performed with hexaminolevulinate. **Results:** 506 patients were includ-

ed: 252 (49.8%) diagnosed with hexaminolevulinate and 254 (50.2%) with white-light endoscopy alone. There were more patients with tumour recurrence, multiple lesions, lesions with a diameter <3 cm, stage Ta disease, and grade 1 lesions in the hexaminolevulinate group. The first quartile median recurrence-free survival time was 310 days in the hexaminolevulinate group and 144 days in the standard-endoscopy group ($p = 0.0015$). **Conclusion:** Hexaminolevulinate was in frequent use in France with specific patient and disease characteristics associated with its use. HOPE illustrates the type of data that can be gained in post-authorisation studies to address requests from European health authorities.

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Introduction

In the European Union (EU) in 2012, 118,280 new cases of urothelial bladder cancer were diagnosed [1]. Non-muscle invasive bladder cancer (NMIBC) accounts

for approximately 75% of newly diagnosed bladder cancers, and 60–70% of NMIBC patients are expected to experience a relapse of the cancers [2]. Outcomes of NMIBC can be optimised with precise risk-stratification of recurrence and progression, adapted adjuvant intravesical treatments and follow-up, but the duration and intensity of follow-up in NMIBC entail high cost-ratios per patient [3, 4]. Endoscopy is the mainstay of diagnosis and surveillance of NMIBC. Compared with standard white-light endoscopy, photodynamic diagnosis (PDD) with blue light and the photosensitiser hexaminolevulinate (Hexvix®; Ipsen, Paris, France) improves the visualisation of bladder tumours, reduces residual tumour rates by at least 20% and improves recurrence-free survival [5–14].

Following the registration of hexaminolevulinate in France, the French authorities asked for more information on routine practices for diagnosis and surveillance of NMIBC. Consequently, the Hexvix® Observational Patients Evaluation (HOPE) study was conducted to determine the distribution of hexaminolevulinate use in the diagnosis of NMIBC, and assess the patient and treatment characteristics associated with different endoscopic modalities (white- or blue-light). This request predated but anticipated the recent change in EU regulations that strongly promote post-authorisation studies across Europe [15, 16].

The HOPE study addresses many of the specific requests listed in the EU regulations (such as the need to generate unbiased efficacy data in the general population and to gather robust information of the use of medicinal products in different sub-populations), and may therefore be a good example of the relevance for clinicians and Health Authorities alike of properly designed observational studies.

Patients and Methods

The study was declared to the appropriate French authorities and all patients received all relevant information and gave consent before inclusion in the study.

Investigator Sites and Patient Selection

In September 2009, the French Health Authority-approved Scientific Committee (D.J., B.M., L.M., A.T., P.J., J.I.) contacted all 50 centres in France that had fluorescence endoscopy equipment available at that time. The centres had to have a minimal experience of 3 months in the use of blue-light endoscopy. The members of the Scientific Committee were excluded from the list of investigators in order to maintain the independent nature of the study.

Fifteen of the contacted centres declined to participate. The target was to include 30 centres in the study. Fifteen centres were

initially included, and this was increased progressively until a maximum of 30 active centres was achieved. The centres were stratified according to the type of healthcare institution, the number of transurethral resections (TUR), and the type of endoscopic equipment to give a good representation of the national spread of centres.

All consenting patients who were candidates for an endoscopy with TUR were eligible. Each centre included the first 20 consecutive patients meeting these criteria. The choice of the technique (standard white-light or blue-light fluorescence endoscopy) was at the discretion of each investigator. Patients were enrolled between November 2009 and November 2011 with the last patient visit in January 2013.

Study Design

The HOPE study was a prospective, observational and non-interventional study. Following inclusion, data collection was ongoing according to the routine practices in each centre. No additional assessments, treatments or other investigations were requested.

The follow-up period was 12 months. Given the duration of the follow-up period, there was a high chance of losing patients to follow-up or of physicians changing jobs. Therefore, regular reminders (e-mail and/or phone call) to participating physicians were scheduled. The results were represented according to the duration of follow-up, that is, less or more than 300 days.

Information Collected

Information was gathered on the type of the participating centre, number of beds, number of beds in the urology department, number of urologists, number of transurethral resection of the bladder (TURB), and equipment available.

At the inclusion visit, patient characteristics (age, gender, Charlson Comorbidity Index), history of disease (first diagnosis or recurrence), exposure to risk factors for bladder cancer, information on TURB and other treatment, and other information on ambulatory care and hospitalisation were all collected. Following the European Association of Urology (EAU) guidelines on NMIBC, the items of the EORTC bladder calculator [17] (presence of carcinoma in situ, number and size of lesions, T stage, grade, recurrence) were collected whenever applicable. At subsequent visits, information was collected as per standard practice at each centre.

Statistics and Sample Size Calculation

The primary endpoint was the proportion of patients with NMIBC who had diagnosis performed with hexaminolevulinate (with 95% confidence intervals [CIs]). The secondary endpoints were comparison between the 2 populations (diagnosis with or without hexaminolevulinate) of patient characteristics, disease characteristics, care management (ambulatory vs. hospitalised care), surgery or medical management during follow-up, frequency of visits, date of first recurrence, occurrence of adverse events, and investigator site characteristics.

Comparisons between the 2 populations used the Student test or Wilcoxon test, or chi-square Fisher's exact test for categorical variables. An exploratory analysis was conducted on the time to recurrence and time to progression in the 2 populations using Kaplan-Meier techniques.

The calculation of the sample size was based on the hypothesis that 20% of the patients would be diagnosed using hexaminolevu-

linated and that 15% of the patients would be lost to follow-up. It was estimated that 600 patients would be needed to obtain a CI of 95% with a precision of 3.5%. The estimation that 20% of patients would be diagnosed using hexaminolevulinate was based upon the Association Française d'Urologie guidelines, which state that the preferential indications of hexaminolevulinate are suspected of high-grade bladder lesions (isolated high-grade cytology without cystoscopic visible lesions) and previous history of high-risk tumours (T1-G3 and/or carcinoma in situ) [2].

Results

Characteristics of Investigator Sites

Fifteen of the 50 centres declined participation, and the data sources could not be verified for 5 centres. Among the 30 centres that were included, 56.7% belong to the public health service (12 university hospitals and 5 general hospitals) and 43.3% to the private health service (11 private hospitals and 2 comprehensive cancer centres). The median (range) number of beds dedicated to urology was 26 (14–54), with a median of 4 (2–8) permanent urologists.

Comparison between Patient Groups

From November 2009 to December 2011, 561 patients were included; 287 (51.2%) were diagnosed with hexaminolevulinate and 274 (48.8%) with white-light (standard) endoscopy alone. In 4 centres, full data monitoring was not possible, and patients from these centres ($n = 55$) were excluded from the analysis. Therefore, 506 patients were retained for assessment: 252 (49.8%) were diagnosed with hexaminolevulinate and 254 (50.2%) with standard endoscopy. Of these patients, 408 (80.6%) were diagnosed with NMIBC (192 and 216 in the hexaminolevulinate and standard endoscopy groups, respectively).

The 2 groups were well balanced for gender, occupational hazard and smoking status (Table 1), but in the group that was diagnosed with the use of hexaminolevulinate, patients were significantly younger and had a better performance status. Significant differences were observed between the 2 groups on the basis of bladder calculator items [17]. In the group that was diagnosed with the use of hexaminolevulinate, there were more multiple lesions, more lesions with a diameter <3 cm, more patients with tumour recurrence, more stage Ta disease and more grade 1 lesions (Table 1). The presence of odds ratio (OR) was similar in both groups.

Before TURB, most patients (69.4%) underwent at least one additional examination with uroculture (45.3%), fibroscopy (52.9%) and cytology (26.7%). Imaging (35.9

and 24.5% had an abdominal ultrasound or computed tomography [CT] scan, respectively) was conducted significantly more frequently in the standard endoscopy group than in the hexaminolevulinate group (abdominal ultrasound: 47.4 and 24.0%, $p < 0.001$; and CT scan: 31.3 and 17.5%, $p = 0.001$, respectively).

Nearly all the patients (99.4%) were hospitalised for TURB with a median duration of 5 days in the standard endoscopy group and 4 days in the hexaminolevulinate group ($p = 0.014$). Cystoscopy was followed by resection of 1–3 lesions in 61.6% of TUR and of ≥ 4 lesions in 37.2% of TUR. Prophylactic antibiotics were prescribed in 50.3% of patients, with 12.3% receiving an early postoperative instillation of mitomycin C (Ametycin).

At baseline, 269 out of 506 (53.2%) patients had a suspected recurrence of bladder cancer (Table 2). The number of previous TURB and time from previous TURB to present recurrence were similar between groups.

Follow-up Exploratory Analysis

The median (95% CI) follow-up of the 408 patients diagnosed with NMIBC was 276 (238–290) days in the hexaminolevulinate group and 184 (148–212) days in the standard endoscopy group ($p = 0.0013$). Of the 408 patients, 361 (88.5%) had at least one urological follow-up visit (median = 2 visits; range 1–6) and 182 (50.4%) had intravesical instillations at follow-up (95/173 [54.9%] in the hexaminolevulinate group and 87/188 [46.3%] in the standard endoscopy group; $p = 0.10$).

The median recurrence-free survival time was not reached during the follow-up of this study. The first quartile median (95% CI) recurrence-free survival was 310 (244–377) days in the hexaminolevulinate group and 144 (113–191) days in the standard endoscopy group (Fig. 1, $p = 0.0015$, log-rank test). The 1-year, recurrence-free survival rate (95% CI) was 54% (42–67%) in the hexaminolevulinate group and 40% (25–53%) in the standard endoscopy group. The use of hexaminolevulinate was not associated with a decrease in the relative risk of muscle-invasive progression (odds ratio [OR] 0.29; 95% CI 0.05–1.54; $p = 0.146$). The risk of recurrence at 1 year was lower in the hexaminolevulinate group than the predicted recurrence rates using the EORTC bladder calculator [17], whereas the observed recurrence rates in the standard endoscopy group were very similar to the predicted rates. The number of patients in the HOPE study with a low risk of recurrence (15% at 1 year) or high risk of recurrence (61% at 1 year) according to the bladder calculator was too low to make a comparison, but among those with an intermediate

Table 1. Characteristics of the 506 assessable patients in HOPE

Characteristics	Total (<i>n</i> = 506)	Hexaminolevulinate		<i>p</i> value
		yes (<i>n</i> = 252)	no (<i>n</i> = 254)	
<i>Patient characteristics</i>				
Gender, <i>n</i> (%)				0.374
Male	416 (82.2)	211 (83.7)	205 (80.7)	
Female	90 (17.8)	41 (16.3)	49 (19.3)	
Age, years				0.018
Median (range)	71 (24–98)	70 (42–92)	72 (24–98)	
ECOG-PS				0.002
0–1	409 (88.3)	221 (92.9)	188 (83.6)	
≥2	54 (11.7)	17 (7.1)	37 (16.4)	
Not documented	43	14	29	
Occupational hazard, <i>n</i> (%)				0.131
Yes	18 (3.9)	6 (2.6)	12 (5.3)	
No	442 (87.4)	227 (90.1)	215 (84.6)	
Not documented	46	19	27	
Smoking status, <i>n</i> (%)				0.82
Smoker	114 (23.6)	59 (24.3)	55 (22.8)	
Previous smoker	226 (46.7)	110 (45.3)	116 (48.1)	
Never smoking	144 (29.8)	74 (30.5)	70 (29.1)	
Not documented	22	9	13	
<i>Disease characteristics</i>				
Bladder calculator items [17]				
Number of lesions, <i>n</i> (%)				<0.001
1	152 (35.3)	51 (25.2)	101 (44.1)	
2–7	252 (58.5)	133 (65.8)	119 (52.0)	
≥8	27 (6.3)	18 (8.9)	9 (3.9)	
Not documented	75	50	25	
Diameter of the main lesion, <i>n</i> (%)				0.002
<3 cm	297 (72.6)	154 (79.8)	143 (66.2)	
≥3 cm	112 (27.4)	39 (20.2)	73 (33.8)	
Not documented	97	59	38	
Recurrence rate, <i>n</i> (%)				<0.001
Primary	229 (53.0)	81 (40.1)	148 (64.3)	
Recurrence ≤1/year	119 (27.5)	74 (36.6)	45 (19.6)	
Recurrence >1/year	84 (19.4)	47 (23.3)	37 (16.1)	
Not documented	74	50	24	
Stage, <i>n</i> (%)				0.002
Ta	267 (69.9)	140 (77.3)	127 (63.2)	
T1	115 (30.1)	41 (22.7)	74 (36.8)	
Not documented	124	71	53	
Grade, <i>n</i> (%)				<0.001
1	112 (26.9)	67 (35.3)	45 (19.9)	
2	147 (35.3)	70 (36.8)	77 (34.1)	
3	157 (37.7)	53 (27.9)	104 (46.0)	
Not documented	90	62	28	
CIS, <i>n</i> (%)				0.67
Yes	69 (15.8)	34 (16.6)	35 (15.1)	
Not documented	69	47	22	
ECOG, Eastern Cooperative Oncology Group; PS, performance status; CIS, carcinoma in situ.				

Table 2. Disease history of relapsing patients

Variables	Total (<i>n</i> = 269)	Hexaminolevulinate		<i>p</i> value
		yes (<i>n</i> = 166)	no (<i>n</i> = 103)	
Previous TUR, <i>n</i>				0.50
Median (range)	2 (0–18)	2 (0–18)	2 (1–10)	
Time from baseline endoscopy and last TUR, months				0.73
Median (range)	13 (1–307)	13 (1–254)	13 (2–307)	
Stage at the previous TUR, <i>n</i> (%)				0.02
Ta	131 (65.2)	90 (72.6)	41 (53.2)	
T1	67 (33.3)	33 (26.6)	34 (44.2)	
T2	3 (1.5)	1 (0.8)	2 (2.6)	
Unknown/NA	68	42	20	
Grade at the previous TUR, <i>n</i> (%)				0.09
Grade 1	47 (22.3)	32 (24.8)	15 (18.3)	
Grade 2	83 (39.3)	55 (42.6)	28 (34.1)	
Grade 3	81 (38.4)	42 (32.6)	39 (47.6)	
Unknown/NA	58	37	21	
CIS, <i>n</i> (%)				0.47
Yes	41 (18.1)	23 (16.7)	18 (20.5)	
Unknown/NA	43	28	15	
Previous instillations, <i>n</i> (%)				0.46
Yes	138 (53.5)	89 (55.3)	49 (50.5)	
Unknown/NA	11	5	6	
If previous instillations, <i>n</i> (%)				0.07
Mitomycin	37 (26.8)	29 (32.6)	8 (16.3)	
BCG	96 (69.6)	58 (65.2)	38 (77.6)	
Mitomycin plus BCG	5 (3.6)	2 (2.2)	3 (6.1)	

TUR, transurethral resection; NA, not applicable; CIS, carcinoma in situ; BCG, Bacillus Calmette-Guérin.

Fig. 1. Recurrence-free survival based on the use of hexaminolevulinate.

risk, the rate of recurrence at 1 year was lower in the hexaminolevulinate group than the standard endoscopy group (OR 0.45; 95% CI 0.22–0.89).

Adverse Events

During the study, 317 patients were exposed to hexaminolevulinate. One patient was hospitalised because of a general status impairment not related to the use of hexaminolevulinate. Twenty deaths were reported: 17 were related to the disease progression, one to a prostate cancer, one to a cardiac failure, and one to severe domestic burns. No death was related to the use of hexaminolevulinate.

Discussion

The recent announcement from the EU [15] will result in a greater frequency of observational studies like the HOPE study in the future. This change in policy reflects calls for more information on the real-world pattern of care and use of medicinal products [18], which is particu-

larly relevant for NMIBC, a prevalent cancer whose management is costly for the community and intrusive for the patient. Indeed, well-designed observational studies may help determine whether the efficacy and tolerability results of randomised clinical trials are reproducible in the more diverse settings and patterns of care in everyday use. The HOPE study was conducted in response to a request from the French Health Authority for more information on routine practices for diagnosis and surveillance of NMIBC.

With regard to efficacy, the increased detection and the decreased recurrence observed in the HOPE study with PDD were consistent with the pivotal trials by Fradet et al. [5] and Grossman et al. [11], and the meta-analysis by Burger et al. [14]. The HOPE study, therefore, provides evidence that PDD use in everyday clinical routine replicates the positive results obtained in the research setting. An improvement in the detection of NMIBC with blue-light cystoscopy with hexaminolevulinate as an adjunct to white-light cystoscopy (versus this technique alone) has also been shown in routine clinical practice in, for example, Spain [19] and Germany [20].

Information about patterns of everyday use makes post-authorisation observational studies crucial for Health Authorities to properly assess and optimise cost-effective cancer care [21]. This is a particular strength of the HOPE study, which provides unexpected but revealing information on the frequency of hexaminolevulinate use in French centres, and on the type of patient selected for diagnosis with hexaminolevulinate. There was more frequent use of hexaminolevulinate in the HOPE study than expected (49.8% compared with the predicted 20%). The estimated frequency was based upon the previous Association Française d'Urologie guidelines indicating the use of hexaminolevulinate when a high-risk lesion was suspected [2], but the European registration of the product provides a broader indication ("in patients with known or high suspicion of bladder cancer"). The more frequent use of hexaminolevulinate in the HOPE study may reflect the recent update of the French guidelines, which recommend the use of hexaminolevulinate for diagnosis at every TURB [22]. This situation may explain why the frequency of use was difficult to predict. Likewise, the impact of instrument capacity or availability on non-use of hexaminolevulinate cannot be estimated from these data. Many patients had previous TURB and this may also have driven the frequency of hexaminolevulinate use; whether more recent data on the use of diffusion-weighted magnetic resonance imaging in the diagnosis of residual cancer before re-TURB [23] will influ-

ence the use of blue-light cystoscopy is difficult to predict. However, these findings from the HOPE study do illustrate how important such post-authorisation studies may be to Health Authorities for making accurate cost-effectiveness analyses (but it should be stressed that no cost-effectiveness analysis was included in the HOPE study). In this example, the greater-than-expected use of hexaminolevulinate may actually have cost-benefits via more accurate guidance for optimising subsequent treatments that can improve outcome [24]. Improved recurrence-free survival with hexaminolevulinate may be associated with an increase in quality-adjusted life years and improved long-term cost effectiveness [25–27].

Another observation on the patterns of use from HOPE was that hexaminolevulinate was used less often in first episodes and isolated lesions, and more often in multiple lesions and in tumours <3 cm and of low stage/grade. There was no particular indication in the EAU guidelines that existed at the time of this trial's commencement that these patient groups should be targeted for diagnosis using hexaminolevulinate [28]. On the other hand, strong recommendations such as urine analysis and urine cytology for the primary assessment of TaT1 bladder tumours [28] were not followed in most patients in the HOPE study. This raises a complex but important question; are there real-life issues that drive more pragmatic practices by the majority of centres and what is the impact of these issues?

The uncertain transition between the research setting and everyday practice spurred the EU to promote post-authorisation efficacy studies, notably when the benefits of the medicinal product may be significantly affected by real-life conditions – which is not the case in the present study – and when the initial efficacy assessment was based on surrogate endpoints. This is appropriate to oncology trials where progression-free survival is widely used as a surrogate as it is often difficult to achieve the appropriate power to detect differences in overall survival, owing to increasing post-progression survival, patient/disease heterogeneity, and variability in the use of active treatments after disease progression [29–31]. Post-authorisation studies, therefore, have the potential to facilitate the introduction of new drugs and new patterns of care (e.g., individualised medicine), opening a promising field of collaboration between the pharmaceutical industry and learned societies such as the EAU, which are in the unique position of federating professionals in Europe across national borders.

One further objective of observational studies is to provide Health Authorities with information on the tol-

Table 3. Some key strengths and drawbacks of observational studies compared with randomised controlled trials

Observational studies	
Strengths	<p>Unbiased assessment of the current management situation vs. RCTs, which have highly controlled populations and tell us nothing about everyday clinical practice.</p> <p>Allows comparison of risks and benefits in “real-life” clinical situations vs. RCTs that have narrow inclusion criteria and standardised treatment regimens that may not reflect the population that will receive the medicinal product post-authorisation or the management decisions made in everyday practice.</p> <p>An idea of what guidelines/labelling is being followed in everyday clinical practice to feed into cost-effectiveness assessments vs. RCTs, which follow strict guidelines that may not reflect what happens in different centres.</p>
Drawbacks	<p>Incomplete information vs. RCTs, which allow the gathering of detailed and complete information at multiple time-points to assess a number of outcomes.</p> <p>Generally no comparator vs. RCTs that can specify the most appropriate comparator (placebo or active treatment) and allow a direct assessment between multiple treatments.</p> <p>Heterogeneous population – but this can sometimes be a strength vs. RCTs that only include the specific population of interest, thus reducing confounding factors on outcomes.</p> <p>No assessment of confounding factors such as centre-effects vs. RCTs that normally adjust findings for multiple confounding factors.</p>
RCT, randomised controlled trial.	

erability of medicinal products when they are used in everyday practice [32–34]. Investigators are encouraged to seek cooperation with Health Authorities, as information from a wide spectrum of patients is needed. HOPE investigators have gathered such information for hexaminolevulinate, thereby confirming the safety profile of this technique in everyday clinical practice.

Other strengths and drawbacks of observational studies are well illustrated by the HOPE study (Table 3). However, one drawback of most observational studies is that they focus on patients receiving a particular medicinal product. The HOPE study is unusual in that 2 groups of patients (those having a diagnosis with or without hexaminolevulinate) were compared. Whether such comparative data can be gained from future observational studies will be determined on a case-by-case basis.

Conclusions

The recent EU regulation to expand the use of post-authorisation studies [15] is aimed at assisting Health Authorities in their assessment of the feasibility and cost-effectiveness of medicinal products in everyday clinical

practice. In future, large-scale and long-term observational studies may be needed to achieve this. The HOPE study was conducted in response to a request from the French Health Authority partly because the management of NMIBC is expensive, because there are no reliable surrogate markers for overall survival, and because endoscopy can have an impact upon outcomes. The increase in detection and the decrease in recurrence observed with PDD in this study were in line with pivotal trials and a meta-analysis.

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Disclosure Statement

The French National Authority for Health (Haute Autorité de Santé) requested that GE Healthcare conduct this study after the registration of Hexvix® on the French market. The authors were selected by GE Healthcare and approved by the French National Authority for Health. All authors received honoraria from GE Healthcare for their work in the design of the study, and for the interim and final analyses. The sponsor was responsible for collection of the data. Since the start of the study, ownership changed and Hexvix® is now sold by Ipsen.

D.J. reports of having received personal fees from GE Healthcare and Ipsen during the conduct of the study and personal fees from Ipsen outside the submitted work. P.J. reports on patent BR-9152. F.R. 1998, licensed to Photocure, and of having received royalties from Photocure to EPFL and CHUV University Hospital, Lausanne, Switzerland. L.M. has no conflicts to disclose. A.T. has no conflicts to disclose. J.I. reports of having received personal fees from Ipsen during the conduct of the study; grants, personal fees and non-financial support from Sanofi; grants, personal fees, non-financial support and other support from Ipsen outside the submitted work. B.M. reports of having received personal fees from GE Healthcare and Ipsen during the conduct of the study.

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