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CLINICAL STUDY

Standardized intraoperative 5-ALA photodynamic therapy for newly diagnosed glioblastoma patients: a preliminary analysis of the INDYGO clinical trial

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Abstract

Purpose Glioblastoma (GBM) is the most aggressive malignant primary brain tumor. The unfavorable prognosis despite maximal therapy relates to high propensity for recurrence. Thus, overall survival (OS) is quite limited and local failure remains the fundamental problem. Here, we present a safety and feasibility trial after treating GBM intraoperatively by photodynamic therapy (PDT) after 5-aminolevulinic acid (5-ALA) administration and maximal resection.

Methods Ten patients with newly diagnosed GBM were enrolled and treated between May 2017 and June 2018. The standardized therapeutic approach included maximal resection (near total or gross total tumor resection (GTR)) guided by 5-ALA fluorescence-guided surgery (FGS), followed by intraoperative PDT. Postoperatively, patients underwent adjuvant therapy (Stupp protocol). Follow-up included clinical examinations and brain MR imaging was performed every 3 months until tumor progression and/or death.

Results There were no unacceptable or unexpected toxicities or serious adverse effects. At the time of the interim analysis, the actuarial 12-months progression-free survival (PFS) rate was 60% (median 17.1 months), and the actuarial 12-months OS rate was 80% (median 23.1 months).

Conclusions This trial assessed the feasibility and the safety of intraoperative 5-ALA PDT as a novel approach for treating GBM after maximal tumor resection. The current standard of care remains microsurgical resection whenever feasible, followed by adjuvant therapy (Stupp protocol). We postulate that PDT delivered immediately after resection as an add-on therapy of this primary brain cancer is safe and may help to decrease the recurrence risk by targeting residual tumor cells in the resection cavity. *Trial registration* NCT number: NCT03048240. EudraCT number: 2016-002706-39.

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Graphic abstract

Keywords Glioblastoma · Photodynamic therapy · 5-ALA · Intraoperative MRI · Clinical trial

Introduction

Glioblastoma (GBM) is a rare neoplastic disease (3–5/100,000 persons) that remains the most frequent and deadly primary malignant brain tumor in adults [1, 2]. The median overall survival (OS) is around 15 months, despite the current standard of care (SOC) [3–5] includes maximal surgical resection whenever possible, followed by chemo- (Temozolomide ®, TMZ) and radiotherapy (RT), e.g. Stupp protocol.

It has been previously acknowledged that complete resection of the enhancing component of GBM is found to impact OS [6, 7]. Recent advances to optimize the extent of resection (EOR) include fluorescence-guided surgery (FGS) with 5-aminolevulinic acid (5-ALA) [7, 8]. 5-ALA has also recently been granted FDA approval for visualization of malignant tumor tissue during glioma surgery in the US [9, 10].

However, the aggressive nature of GBM tumors almost always results in local tumor recurrence in up to 90% of patients [11]. Improvement of local control after surgery by adjuvant therapy delivered intraoperatively could potentially impact patient's OS. Intraoperative PDT may permit targeting of residual tumor cells at the infiltrative margin after 5-ALA FGS. Photodynamic therapy actually relies on a photochemical reaction occurring after the laser light activation of the photosensitive 5-ALA metabolite, protoporphyrin IX (PpIX), which results in the release of free radicals, including singlet oxygen species. The intracellular accumulation of PpIX and free radicals [12] can lead to a very local tumor cytotoxic effect sparing normal cells [13–15].

Based on our preclinical data [16–18] and prior human studies with 5-ALA intraoperative PDT in the multimodal management of GBM [14, 19–21], we initiated a pilot prospective, nonrandomized study (INDYGO). Our approach included, for the first time, a standardized therapeutic 5-ALA PDT performed after maximal tumor resection followed by SOC treatment for newly diagnosed GBM. The primary aim was to evaluate the feasibility and safety of intraoperative PDT with a dedicated device for newly diagnosed GBM. Patients underwent 5-ALA FGS, standardized 5-ALA PDT, followed by the Stupp protocol.

Materials and methods

Study design

This study was designed as prospective, single-center, non-randomized pilot study (Lille University Hospital, France). Ten patients were enrolled with newly diagnosed GBM.

All procedures were performed in accordance with the ethical standards of the National Research Committee and the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The French National Agency for Medicine and Health Product Safety (ANSM) as well as the French National Ethics Committee approved this study. Informed consent was obtained from all of the involved participants.

Inclusion criteria

The inclusion criteria were as follows: (1) high probability of GBM according to radiological criteria; (2) surgical indication determined in a multidisciplinary neuro-oncology consultation meeting; (3) resectability; and (4) eligibility to undergo the SOC after surgery. Other inclusion criteria were as follows: (1) age of 18 years or older; (2) Karnofsky Performance Status (KPS) score of 70 or higher; and (3) absence of contraindications to MRI.

Exclusion criteria

The main exclusion criteria were contraindications to 5-ALA administration (hypersensitivity to 5-ALA hydrochloride or porphyrins, inadequate renal or hepatic function; acute or chronic types of porphyria, or pregnancy,) or MRI procedures and multifocal disease.

Study participants

Between May 2017 and June 2018, 10 patients with surgically accessible lesions for maximal resection were enrolled. After the enrollment of first five patients, an Independent Safety Monitoring Board (ISMB) met in December 2017 and authorized the completion of the study with the inclusion of five more patients.

Baseline patient characteristics

The baseline patient characteristics (see Table 1 for details) were similar to those in previously published studies in terms of epidemiology [22, 23]. The median age was 57.1 years [35–69.3], 70% of the patients were male, and the median KPS score was 85 (range 70–100). Eight patients underwent GTR of their tumor.

Primary aim

The primary aim was to assess the feasibility and safety of the intraoperative 5-ALA PDT with a dedicated device in patients with newly diagnosed GBM accessible for surgical removal utilizing 5-ALA FGS.

Secondary aim

Secondary aims were measures of PFS (from the date of diagnosis until the date of defined relapse) and OS (from the date of diagnosis until the date of death).

Intraoperative standardized PDT description

Screened patients underwent FGS with 5-ALA orally administered at 20 mg/kg body mass (Gliolan®, Medac GmbH, Wedel, Germany) 6 h before surgery to allow the surgeon to achieve maximal gross tumor resection with FGS [24].

All patients (n = 10) underwent a high-field intraoperative MRI (iMRI) (General Electric Medical System, Optima 450MRw) examination before the PDT procedure to assess the initial EOR. This MRI examination included gadolinium-enhanced T1 (T1Gd) and Fast Imaging Employing Steady-state Acquisition (FIESTA) diffusion and perfusion sequences. Depending on the findings with iMRI, a second stage of microsurgical resection was performed in cases of residual contrast enhancement amenable to further resection.

A balloon illumination device [25, 26] recently designed in our university hospital by our team to fit in the surgical resection cavity was used to evaluate the feasibility of intraoperative PDT (for details, see Fig. 1) after tumor resection. Laser light exposure during the PDT procedure was performed by means of this dedicated illumination device connected to a 3 W laser system (CERALAS^{TM} PDT 635, Biolitec, Jena, Germany). The laser system, optic fibers, and illumination device were prepared and assessed before each treatment. After the surgeon had placed the device in the surgical cavity (Fig. 2), the device was inflated with a light diffusion fluid to fill the balloon and conform to the shape of the resection cavity. Using a dedicated algorithm [26], the illumination duration was then automatically computed from the volume of the tumor so that the cavity wall received 200 J cm^{-2}. Finally, the total dose was delivered with 5 fractions (alternating laser on/laser off with an off period of 2 min) as evaluated in preclinical experiments [16–18, 27–29].

Early after PDT delivery, a second intraoperative MRI examination utilizing the same sequences described prior to PDT application was performed to assess the potential acute effects or toxicity of PDT on the surrounding brain tissue of the resection cavity.

Table 1 Patient baseline characteristics and time from diagnosis to recurrence and/or death (or from diagnosis to the latest follow-up if free from recurrence and/or still alive)

Patient	Age (years)	KPS	Sex	Gross total resection according to last iMRI	Second stage of microsurgical resection after first iMRI	Remaining fluorescence*	Location	Tumor volume (cm^3)	Diffusing balloon volume (cm^3)
#1	55.4	70	F	Y	N	Vague	Temporal left lobe	21	54
#2	56.6	100	M	Y	N	No	Right frontal lobe	41.6	59
#3	44.8	90	M	Y	N	No	Right frontal lobe	83.2	110
#4	68.4	80	M	N	Y	Vague	Temporal right lobe	77.9	95
#5	54.5	90	F	N	Y	Bright	Temporal right lobe	41.8	30
#6	64.1	70	M	Y	N	No	Temporal right lobe	37.4	50
#7	69.3	80	M	Y	N	No	Right occipito-temporal junction	27.2	43
#8	58.1	90	M	N	Y	Vague	Right frontal lobe and corpus callosum	78	80
#9	57.6	100	F	Y	N	No	Temporal left lobe	10.5	30
#10	35.1	80	M	Y	Y	No	Right frontal lobe	74.6	80
Median	57.1	85		Yes, No	Yes, No	Bright, No, Vague			

Patient	MGMT Methylation	IDH mutation	Completed radiotherapy (Gy)	Concomitant temolomide (weeks)	No. of maintenance TMZ cycles until first tumor progression	Progression Free Survival (months)	Relapse	Overall Survival (months)	Second/third lines treatment post relapse
#1	4.50%	No	60 Gy	6	5	9.6	Remote	20.6	Radiation therapy (3 × 9 Gy) + lomustine/bevacizumab
#2	2%	No	60 Gy	6	2	6.2	Remote	10.0	Radiation therapy (60 Gy) + temozolomide/bevacizumab + lomustine
#3	1%	No	60 Gy	6	6	8.3	Local	15.1	Bevacizumab + fotemustine
#4	18%	No	60 Gy	6	6	17.3	Local	20.5	Temozolomide
#5	4%	No	60 Gy	6	6	18.5	Remote then local progression	25.6	Bevacizumab + lomustine/ABT414 + temozolomide
#6	31%	No	60 Gy	6	6	*35.7*	N/A	*35.7*	N/A
#7	4%	No	60 Gy	6	6	*33.5*	N/A	*33.8*	N/A
#8	2%	No	60 Gy	6	4	8.7	Local	9.6	Bevacizumab + lomustine

Table 1 (continued)

Patient	MGMT Methylation	IDH mutation	Completed radiotherapy (Gy)	Concomitant temolomide (weeks)	No. of maintenance TMZ cycles until first tumor progression	Progression Free Survival (months)	Relapse	Overall Survival (months)	Second/third lines treatment post relapse
#9	13%	No	60 Gy	4	0	16.9	Local	*32.5*	Surgery FGS + Gliadel + temozolomide
#10	57.20%	IDH1/IDH2	60 Gy	6	6	*29.7*	N/A	*29.7*	N/A
Median						17.1		23.1	
					* Free of recurrence at the latest monitoring		* Alive at the latest monitoring		

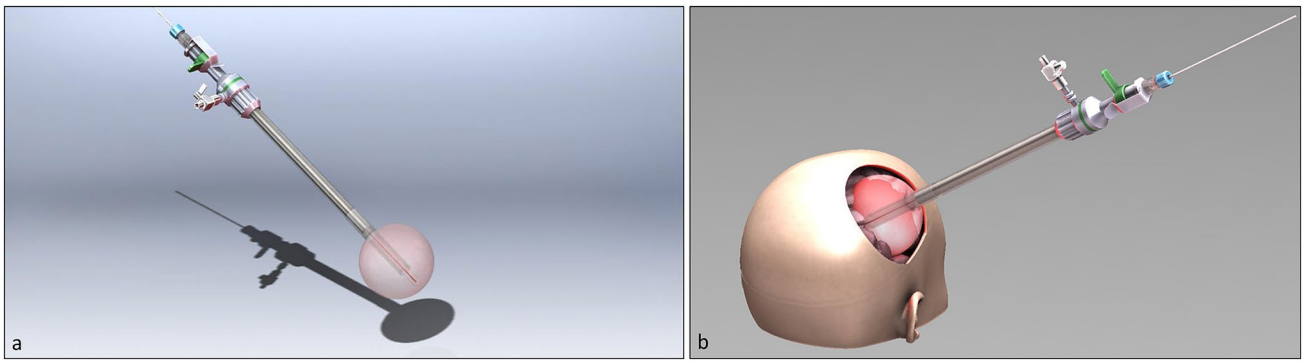


Fig. 1 **a** 3D view of the illumination device designed for this study. **b** A balloon was inserted in the cavity and inflated to fit the shape of the cavity in such a manner that light diffusion was homogenous throughout the cavity. Light was emitted through an optical fiber connected to the medical laser device and diffused within the balloon

Anatomopathological diagnosis

All patients had paraffin-embedded tumor tissue available for evaluation of the O6-methylguanine-DNA methyltransferase (MGMT) gene promoter methylation status [30] and IDH mutation status, by a central laboratory, which was the same for every individual patient, located at our University Hospital.

Initial postsurgical therapeutic approach

After completion of the FGS and PDT, patients underwent treatment with the Stupp protocol including fractionated RT and concurrent and adjuvant TMZ. A total of 60 Gy was administered (30–33 fractions of 1.8–2 Gy) with daily TMZ chemotherapy (75 mg/m^2/day). The patients underwent standard maintenance TMZ chemotherapy (150–200 mg/m^2/day for 5 days every 28 days) for 6–12 cycles according to the protocol from the ESMP [31, 32].

Patient assessment and follow-up

The initial postoperative MRI assessment was acquired within 48 h after surgery. Patients were seen monthly for medical follow-up and adjuvant therapy up to 9 months and then quarterly thereafter until tumor recurrence was determined. Fifteen visits were scheduled during the follow-up course. Each visit included a complete clinical examination. MRI assessments included T1 Gadolinium-injected and fluid-attenuated inversion recovery (FLAIR) sequences and were acquired before microsurgery, after microsurgery and before RT, 4 weeks after RT and then on a quarterly basis.

Adverse events (AEs) were recorded prospectively according to the National Cancer Institute's Common

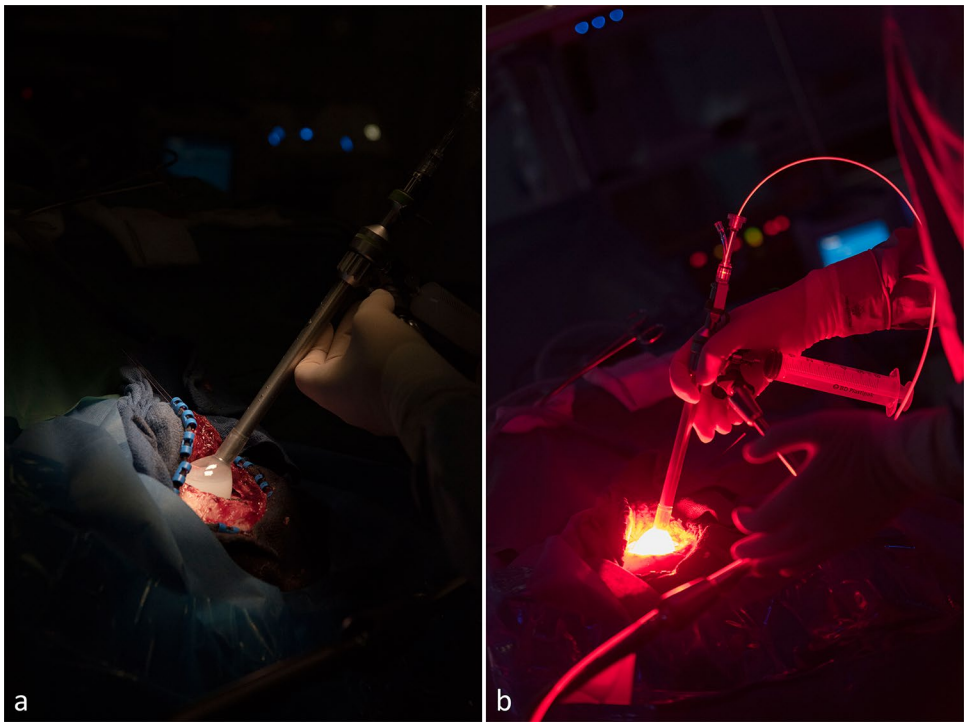


Fig. 2 **a** and **b** Set-up of the illumination device in the surgical cavity with the laser on; light transported from the laser to the balloon through the optical fiber can be seen

terminology Criteria of Adverse Events (NCI-CTCAE, version 4.0). AEs were recorded from the date of screening until 30 days after surgery and PDT. AEs were reviewed by the ISMB.

Outcome measures

The primary outcome measure was the number of patients undergoing the full intraoperative PDT procedure with unacceptable or unexpected toxicity (grade ≥ 3), graded according to the NCI-CTCAE (version 4.0). The time frame considered was from the administration of 5-ALA (20 mg/kg body weight) until 1-month post-PDT. In particular, the following complications were investigated: hemorrhage, infection; new neurological deficit(s) responsible for severe disability; status epilepticus; and death during the postoperative period. The target was that at least 6 of 10 patients benefited from complete PDT without unacceptable or unexpected toxicity (noninferiority study).

Tumor progression and further therapy

When patients experienced tumor progression, a second-line treatment strategy (chemotherapy, repeat RT, and/or second microsurgical resection, whenever feasible) was discussed during a multidisciplinary neuro-oncology consultation meeting.

Local GBM recurrence or relapse was evaluated by standard and regular MRI examinations according to the Response Assessment in Neuro-Oncology (RANO) criteria [33].

Statistics

Survival analysis from the time of diagnosis to tumor progression, death or latest follow-up were plotted according to the Kaplan–Meier method. Patients were censored at the last follow-up or at the time of death.

Results

Standardized PDT delivery

All patients had completed standardized PDT in the operative theater immediately after the 5-ALA FGS. The median

Table 2 Light exposure characteristics of PDT delivery

	Median	Range
Total light exposure duration (minutes)	10	[7–16.5]
Additional surgery time (minutes) *(set-up/light-on/light-off)*	35	[20–48]
Total light dose delivered (Joules)	1772	[1163–2736]

light exposure duration was 603 s [417–980] (for details see Table 2).

Further management of the patients consisted of the conventional Stupp protocol; all patients but one completed the entire regimen of fractionated RT and concomitant TMZ treatment followed by adjuvant TMZ treatment.

PFS and OS

At the latest follow-up, six patients were deceased, and four were still alive, one of whom faced recurrent disease. Forty-two percent of the recurrent foci were distant from the initial GBM location. Figure 3 illustrates the case of remote relapse relative to the surgical cavity. Figure 4 illustrates the case of patient free of recurrence 22 months after surgery.

Table 1 reports preliminary efficacy endpoints. PFS estimated at the latest follow-up showed a median time from diagnosis to relapse of 17.1 months. Similarly, the estimated median OS indicated almost 23.1 months of survival.

Figure 5 illustrates the Kaplan–Meier curves plotted according to data collected at the latest follow-up for each individual (among surviving patients) and at the time of death (among deceased patients).

Safety and individual tolerability

No AEs related to the addition of intraoperative PDT were observed during the monitoring of the patients. Our ISMB has concluded that the addition of the PDT procedure during the surgery in patients with newly diagnosed glioblastoma was not associated with any significant adverse or toxic effects.

Main serious adverse events (SAEs) not related to PDT and recorded during the study are presented in Table 3. These SAEs were coded according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) MedDRA dictionary [34].

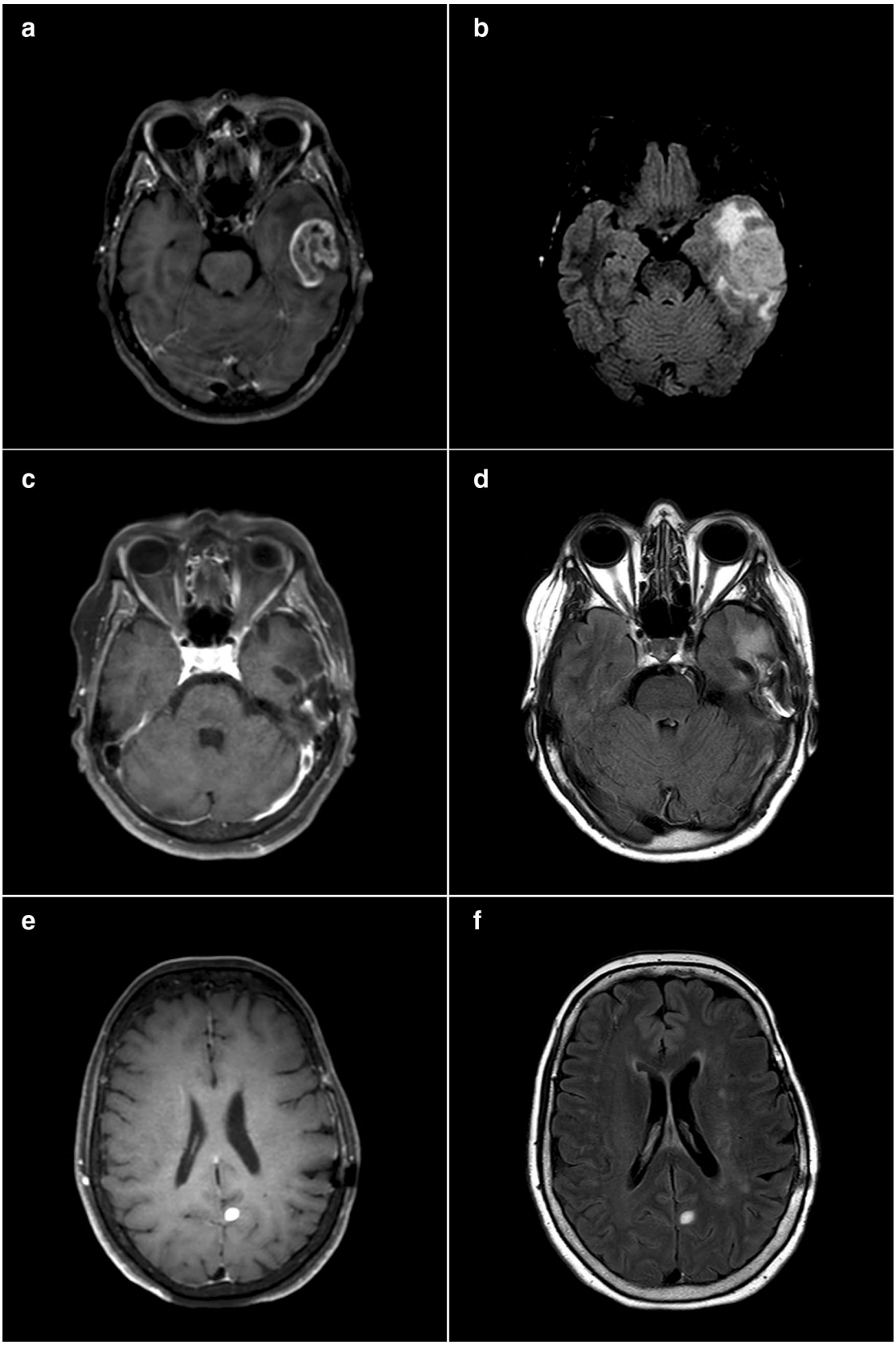
Discussion

In our study we evaluated the feasibility and safety of standardized intraoperative PDT immediately after maximal tumor resection using 5-ALA FGS and confirmed by iMRI. Moreover, after intraoperative PDT, a second iMRI was performed to exclude any potential treatment toxicities. We report no unacceptable or unexpected toxicities after 5-ALA administration and after intraoperative PDT with follow-up for up to 24 months. Concerning the efficacy endpoints, four of the ten patients enrolled continue to be followed, with one of them facing relapse. Thus, at this stage, the median PFS (17.1 months) and the median OS (23.1 months) were evaluated according to the latest monitoring time point. Interestingly, only less than 60% of the sites of tumor recurrence (4/7) were localized adjacent to the tumor bed, while 85% of tumor relapse sites are usually reported located at the resection margins [11].

Despite numerous therapeutic advances, GBM remains the most aggressive and lethal primary brain tumor. EOR is one of the key factors related to prognosis [35, 36], following age and KPS score prior to surgery. However, except for the recent FDA approval of 5-ALA for FGS and costly techniques, such as iMRI [37], new and innovative technologies and devices to support neurosurgeons in improving the local control of the disease have been scarce.

Intraoperative PDT as a potential treatment for malignant brain tumors was initially reported in 1987 by Kostron et al. [38]. Fourteen patients were evaluated and benefitted from intravenous, intraarterial or direct intratumoral injection of Photofrin. In only 8 cases, this protocol included a single dose of 4-Gy ionizing radiation. The authors reported no toxicity and concluded that intraarterial and direct intratumoral injection of the photosensitizer was feasible. In a second non controlled trial in 1988, Kostron et al. [39] included 20 patients with heterogenous pathologies (18 GBM, 1 meningioma, 1 melanoma metastasis). After PDT, 16 cases underwent single dose radiation of 4 Gy of fast electrons. Moreover, 8 patients underwent conventional radiotherapy. Five cases suffered from phototoxicity to the skin. The authors concluded that PDT might be a valuable option. More recently, in 1994, Kostron et al. [40] reviewed their experience on a heterogenous cohort of 58 cases, most of whom were glioblastomas (11 primary and 39 recurrent), but also malignant meningiomas and brain metastasis. The authors concluded that PDT prolonged survival of primary GBM significantly and doubled the survival of recurrent high-grade gliomas. Of note, such studies were performed using a heterogenous protocol in the absence of Stupp protocol and before the new era of molecular diagnosis, which completely shifted our understanding of primary brain tumors and particularly GBM.

The positive interpretation of the PFS and OS of the present prospective cohort has to be made cautiously, since only a limited number of patients were included, with GBM tumors amenable to maximal gross total resection (GTR). Of note, almost all patients in the present series had unmethylated MGMT or low MGMT promoter methylation, that has been associated with poor outcomes in glioblastoma patients [30]. Four of our patients with low MGMT promoter methylation had extended OS in comparison with the OS usually reported in the literature for this population of patients who may not respond well to TMZ [30, 41]. In particular, among the ten patients enrolled, one patient (#7) (Fig. 4) exhibited many of the poorest prognostic factors, including elderly age, lower KPS score, and molecular markers, such


a
b
c
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e
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◂**Fig. 3** MRI studies, including **a** T1Gd and **b** FLAIR sequences, of patient #1 before treatment. **c** T1Gd and **d** FLAIR examinations at the time of the relapse, 9 months postsurgery, showing the surgical cavity still free of recurrence. **e** T1Gd and **f** FLAIR examinations showing recurrence in the internal left parietal area

as low MGMT promoter methylation, gain of chromosome 7 (EGFR amplification) and loss of chromosome 10 (PTEN deletion). Despite this context, patient #7 is still alive and free of recurrence 25 months after surgery. However, the present study was not designed to address efficacy of

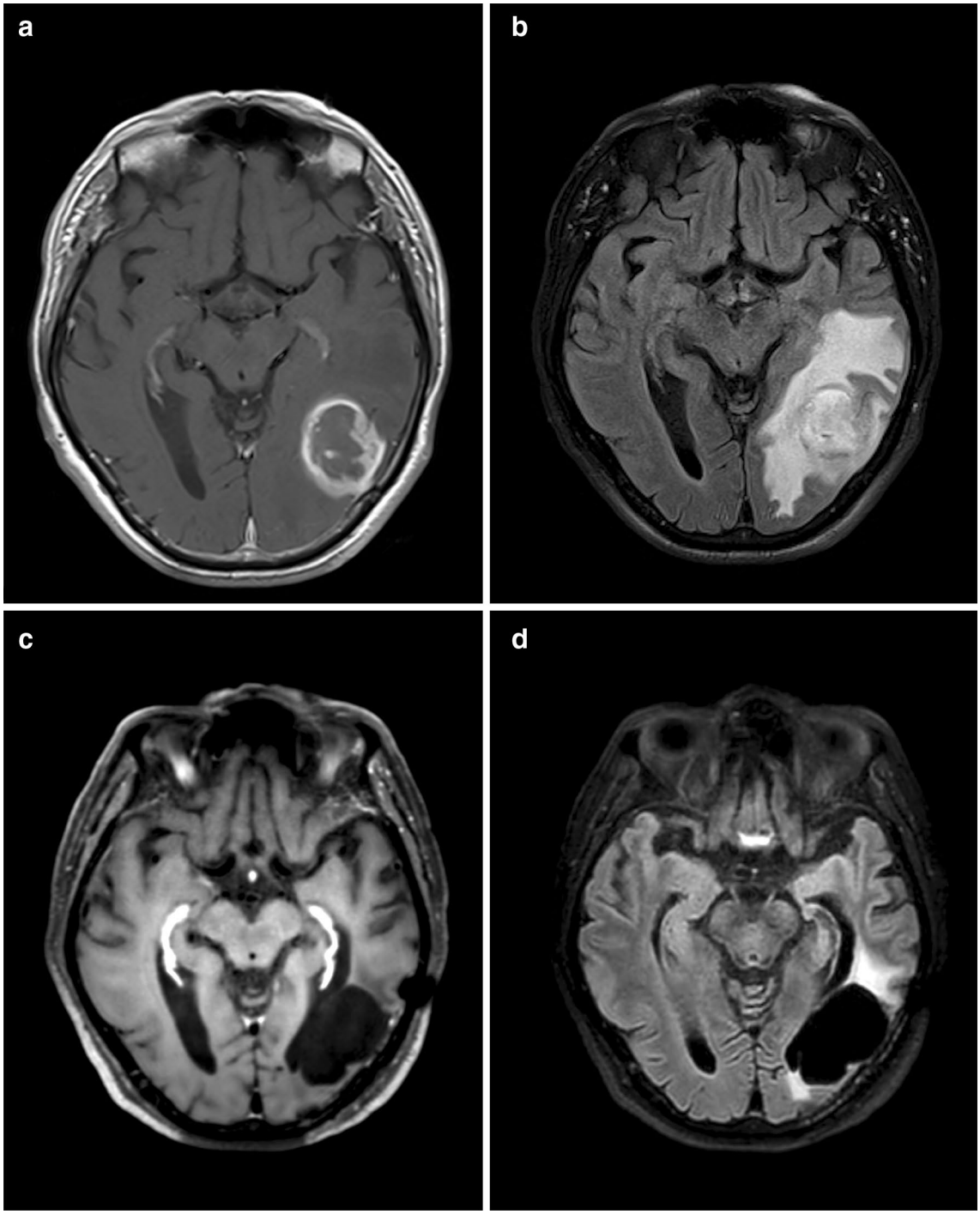

Fig. 4 MRI studies, including **a** T1Gd and **b** FLAIR sequences, of patient #7 before treatment. Posttreatment **c** T1Gd and **d** FLAIR examinations showing the surgical cavity still free of recurrence 22 months after surgery despite poor prognostic factors (age, KPS score, unmethylated MGMT promoter status, chromosome 7 gain, chromosome 10 loss)

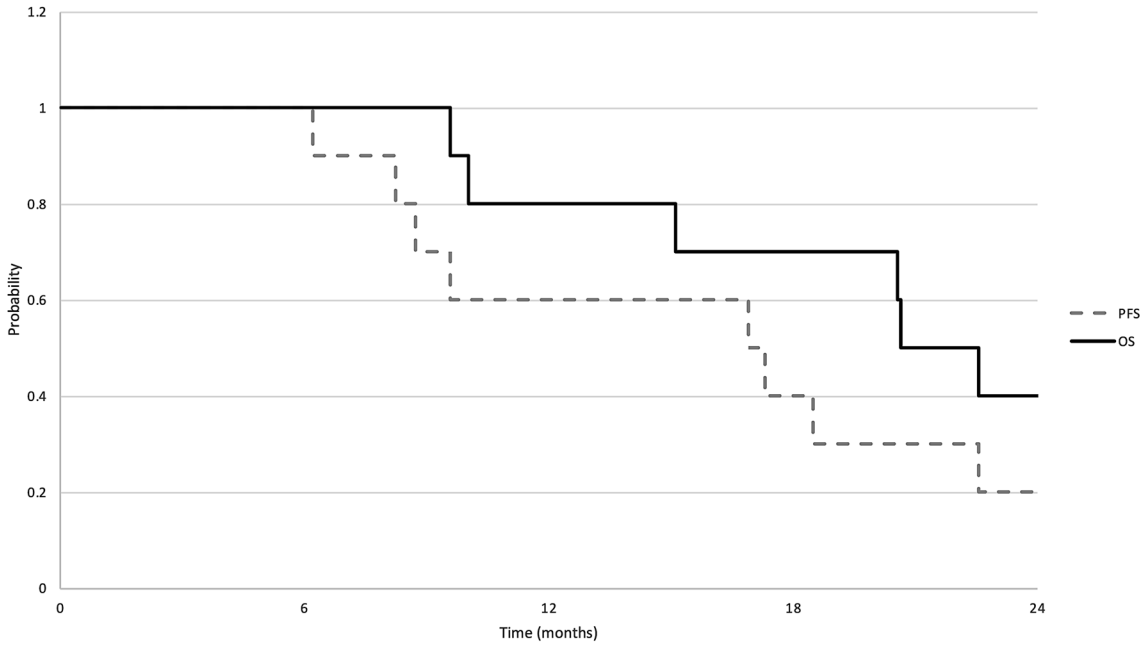

Fig. 5 Survival Kaplan-Meier curves for patients included plotted from data collected at the latest monitoring

intraoperative PDT. Thus, the data presented in terms of both OS and PFS were secondary objectives.

If we consider the patients who had a short progression-free survival, less than 10 months (patients #1; #2; #3; #8), two of them initially presented with a distant recurrence. Patient #2 presented with a contralateral recurrence and died of leptomeningeal tumor progression. Nevertheless, patient #1, who presented with a distant recurrence and an unmethylated status, had an OS over 20 months. Patients #3 and #8, died due to local tumor progression of their disease.

We believe a strength of the present trial was the confirmed feasibility of a standardized and reproducible protocol for intraoperative PDT delivery. We found that a dose deposit of 200 J.cm^2 at the balloon wall was determined to ensure the deposit of at least 25 J.cm^{-2}, which we found to be the cytotoxic dose in our preclinical studies [16–18], within the first 5 mm of the cavity wall. The impact of a higher dose deposit greater than 200 J.cm^{-2} will be considered in a future dose escalation trial, to evaluate how it might (or not) further impact local recurrence (e.g. depth of relapse from cavity wall, local versus remote relapse) (https://clinicaltrials.gov/ct2/show/NCT04391062?term=dosindygo&draw=2&rank=1). While we designed our clinical study to ensure 5 mm penetration of the dose deposit with PDT, we acknowledge that infiltrative tumor cells can extend out further from the tumor cavity, which is difficult to confirm on preoperative MRI. Other local treatments that have been described, such as Carmustine wafers [42, 43], are limited to smaller penetration of surrounding brain tissue (approximatively 1 mm), due to the reliance of chemotherapy diffusion, leading to probable efficacy limitations [44].

The implementation of intraoperative PDT with the device developed for this study [45] was designed to be easily usable with reproducible treatment dosimetry. Intraoperative PDT with this device was confirmed to be feasible and safe with acceptable additional surgery time. Indeed, a median additional time of 30 min was tolerated by the patient and the surgical team in the context of such surgery. Short training sessions prior to the first PDT treatments were necessary, indicating that neurosurgical teams could implement intraoperative PDT in addition to FGS which is routinely performed by neurosurgeons in their daily practice.

During the trial, numerous markers were monitored to assess PDT feasibility and safety and explore meaningful data for further clinical trials aiming at evaluating PDT efficacy. Among them, MRI examinations were performed immediately after tumor resection (before PDT), early after PDT (within 1 h postoperatively) to highlight the potentially acute effects of PDT, and within 48 h after treatment. However, no significant differences were observed between pre- and post-PDT MRI examinations. In this small cohort, we did not find specific changes, other than in the context of well described post-surgery and chemoradiotherapy changes. In our immediate postoperative scans, we did not visualize such changes. In animal studies, some authors revealed prolonged T2 relaxation times (MRI T2 values) in images from tumor-free animals acquired at days 2, 10, 28 post PDT, suggesting thus the presence of free water protons which were not associated

Table 3 Main SAEs not related to PDT and coded according to the ICH MedDRA dictionary including Lowest Level Terms (LLTs) and the System Organ Class (SC)

Patient	Seriousness criteria	Reaction/event as reported by primary source in Native Language	Reaction/event in MedDRA terminology (LLT)	Reaction/event in MedDRA terminology (SC)	Outcome of reaction/event at the time of last observation	Start of reaction / event (in Days after surgery)	End of reaction/event (in Days after start)	Severity
#2	Hospitalization or prolongation of existing hospitalization	Hospitalization caused by recurrent rapid atrial fibrillation	Recurrent atrial fibrillation	Cardiac disorders	Recovered/resolved	22	5	3 (Serious)
#4	Other medically important condition	Carcinoma epidermoid	Carcinoma epidermoid	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Not recovered/not resolved	43	–	3 (Serious)
#8	Hospitalization or prolongation of existing hospitalization	Admitted in Neurosurgery 2 weeks postoperative because of fluid leakage from the scar—(afebrie, leakage of a clear fluid, scar clean, no cephalalgia)	Postoperative discharge	Injury, poisoning and procedural complications	Recovered/resolved	14	0	1 (Mild)
#9	Other medically important condition	Suspected BACTRIM related toxicoderma leading to stop Bactrim the day after	Toxicoderma	Skin and subcutaneous tissue disorders	Not recovered/not resolved	88	–	2 (Moderate)
#9	Hospitalization or prolongation of existing hospitalization	Iatrogenic bicytopenia (thrombocytopenia, without bleeding) leading to stop Temozolomide	Bicytopenia	Blood and lymphatic system disorders	Not recovered/not resolved	78	–	3 (Serious)
#8	Death	Partial epilepsy caused by a glial lesion recurrence	Partial epilepsy	Nervous system disorders	Fatal	240	31	5 (Death)

with structural proteins. It was further suggested that such is characteristic of edema and inflammation. An inverse correlation between PDT-induced inflammation and animal survival was noted, which was considered similar to benefits from steroids alleviating inflammation and potentially resulting in longer survival [46] While iMRI was used during surgery for safety studies of any adverse effects or toxicities related to intraoperative PDT, this approach does not need to be utilized in future studies where centers do not have iMRI technology. Overall, we did not encounter any intraoperative safety issues after PDT in our patient population.

It also seems to us that intraoperative PDT may be a good treatment option for recurrent GBM cases. In fact, recently, Schipmann et al. [20] evaluated PDT for such patients, utilizing a non-standardized PDT delivery with promising results.

Our study has several inherent limitations. One is the small number of cases enrolled in our single center trial. Here, we evaluated the feasibility and safety of this procedure after preliminary data which were obtained in preclinical animal studies at our institution. In this sense, we did not note any particular AEs related to PDT. A second limitation is the absence of a control arm. The study design was clearly constituted to test the safety and feasibility of this procedure. In this sense, we did not conceive, at baseline, two different study arms. A third limitation is related to potential biological heterogeneity (MGMT methylation) inside the cohort. However, we did not restrict patient enrollment in this trial based on prognostic indicators which could have induced further bias. A fourth limitation is related to the lack of further tissue analysis after PDT therapy. We are not able to conclude, at this point, whether PDT was inducing additional and/or increased apoptosis.

Conclusion

This INDYGO trial assessed the feasibility and safety of intraoperative 5-ALA PDT, a novel seamless approach for treating GBM. This approach was applied, for the first time with 5-ALA, in the frame of a standardized, one session, intraoperative PDT delivery by an in-house dedicated device, which was found to be safe. The efficacy of such a new therapeutic approach performed after maximal 5-ALA FGS has to be further evaluated in clinical trials with a larger number of patients.

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Availability of data and material The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability Not applicable for that section.

Declarations

Conflicts of interest M. Vermandel, C. Dupont, S. Mordon and N. Reyns are co-founders of Hemerion Therapeutics SAS, Lille, France. Constantinos Hadjipanayis is a consultant for NX Development Corporation (NXDC) and Synaptive Medical Inc. He receives royalties from the sale of Gleolan® (5-ALA) which is marketed by NXDC. Gleolan® is an optical imaging agent approved in the United States for the visualization of malignant tissue during glioma surgery.

Consent to participate All subjects signed a written informed consent form.

Consent to publish All subject authorized the publication anonymously of their data.

Ethical approval All procedures performed in studies were in accordance with the ethical standards of the National Research Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The French National Agency for Medicine and Health Product Safety (ANSM) as well as the French National Ethics Committee approved this study.

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