



# Partial splenic embolization with Glubran<sup>®</sup>2/Lipiodol<sup>®</sup> mixture for oncological patients with hypersplenism-related thrombocytopenia requiring systemic chemotherapy

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**Background:** Partial splenic embolization (PSE) has been used to improve thrombocytopenia related to hypersplenism. The optimal embolic agent is still debated. The purpose of this study was to evaluate the safety, hematologic response and outcomes of PSE with cyanoacrylate glue for oncological patients with hypersplenism-related thrombocytopenia requiring systemic chemotherapy (SC).

**Methods:** Retrospective single-center observational report of cancer patients with thrombocytopenia related to hypersplenism and requiring SC who underwent PSE with N-butyl cyanoacrylate-methacryloxy sulfolane (NBCA-MS) Glubran<sup>®</sup>2 glue between February 2015 and September 2017. All patients were treated under local anesthesia with a Glubran<sup>®</sup>2/Lipiodol<sup>®</sup> mixture of 1:5 ratio. They all received empiric antibiotic coverage. Splenic volume and parenchyma infarction rate were evaluated by CT scan within 1 month of PSE. Primary and secondary endpoints of the current study included a platelet count increase  $>150 \times 10^9/L$  and the initiation of SC, respectively. Periprocedural laboratory values and adverse events were recorded.

**Results:** PSE was performed in eight patients (6 males, 2 females; median age, 59 years; range, 33–75 years) for a technical success of 100%. For procedures with adequate follow-up, primary and secondary endpoints were achieved in 100% (7 of 7 patients) and 100% (7 of 7 patients) of patients, respectively. One patient died before follow-up, unrelated to the procedure. Mean splenic infarction post-PSE was 55% (range, 21–70%) on CT scan. For 7 patients with laboratory follow-up, the mean platelet count significantly increased from  $74 \times 10^9/L$  [range,  $(62-83) \times 10^9/L$ ] immediately before PSE to a peak level of  $272 \times 10^9/L$  [range,  $(161-417) \times 10^9/L$ ] 10 days after PSE ( $P < 0.05$ ). All patients could receive SC after PSE. No non-target glue embolization occurred. All patients experienced a transient and moderate postembolization syndrome. No severe postembolization syndrome occurred. No major complication was reported. The mean overall survival was 7.9 months (range, 0.6–10.4 months) among the 8 patients after PSE.

**Conclusions:** PSE with cyanoacrylate glue is safe and effective in the management of thrombocytopenia related to hypersplenism in cancer patients. It allows sufficient platelet count improvement for administration of SC.

**Keywords:** Partial splenic embolization (PSE); hypersplenism; thrombocytopenia; cyanoacrylate glue; systemic chemotherapy

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## Introduction

Thrombocytopenia related to hypersplenism is seen in a variety of clinical settings, the most common being portal hypertension and splenomegaly due to cirrhosis (1,2). Thrombocytopenia of hypersplenism, defined as a platelet count below  $75 \times 10^9/L$ , is predominantly caused by increased splenic sequestration or the destruction of platelets (1). In oncological patients, hypersplenism can occur as a result of hepatic injury secondary to chemotherapy drugs, and thrombocytopenia can preclude or limit administration of systemic therapy (2-5). Platelet transfusion, which remains the most effective method of correcting thrombocytopenia, has temporary and limited effects in patients with an increase in platelet sequestration and destruction (6,7). Then, splenectomy is often considered as a last resort to treat refractory thrombocytopenia. However, surgical treatment is risky and often times contra-indicated in such poor candidates (8,9). Over the past 2 decades, partial splenic embolization (PSE) has been used to safely palliate the effects of hypersplenism by reducing the volume of splenic parenchyma (2-6). Although the efficacy of PSE for relieving thrombocytopenia is well-established, the optimal embolic agent to be used remains to determine (10-14). Various embolic materials have been used for PSE, including temporary agents such as absorbable gelatin sponge particles and permanent agents such as calibrated microspheres. All of these agents, however, are associated with a severe postembolization syndrome that often persists over 1 week. Liquid embolic agents, especially cyanoacrylates, may be very useful in such a setting, thanks to their properties (15). N-butyl cyanoacrylate-methacryloxy sulfolane (NBCA-MS; Glubran®2; GEM Srl, Viareggio, Italy) is a well-known glue comprising a proprietary comonomer, making the glue more stable. This is the only glue approved by the European Community for internal human use. This synthetically derived glue shows rapid polymerization (1-5 s), but complete sealing occurs in approximately 5 min. The use of Lipiodol® (Guerbet, Aulnay-sous-Bois, France) is mandatory to make the glue radiopaque and modulate the delay of polymerization. To our knowledge, the use of glue in such a setting has not been reported.

The purpose of the current study was to evaluate the safety, feasibility and effects on platelet count of PSE with Glubran®2/Lipiodol® mixture for oncological patients with hypersplenism-related thrombocytopenia requiring systemic chemotherapy (SC).

## Methods

### *Study population*

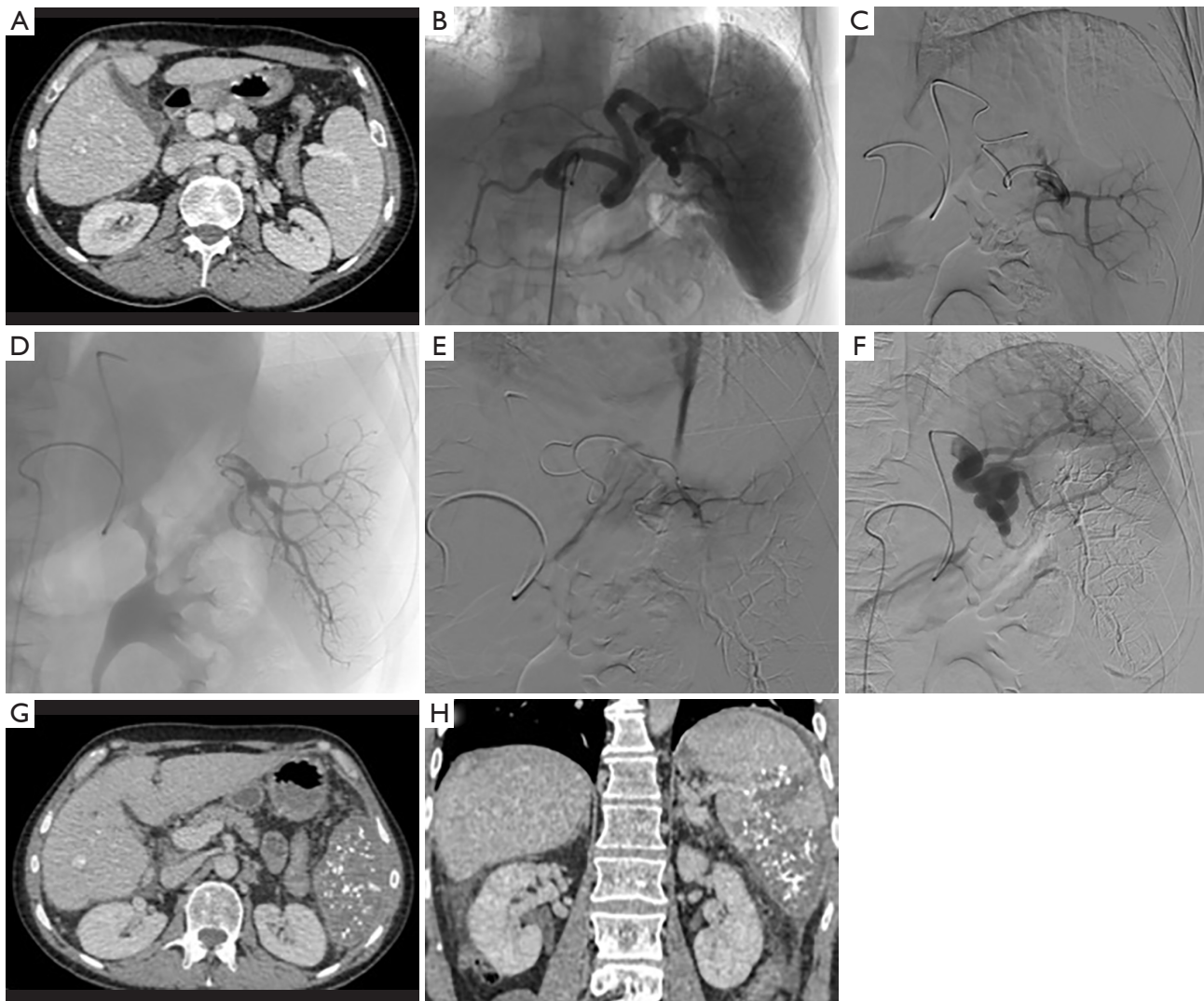
Retrospective single-center review of all cancer patients with chemotherapy-induced thrombocytopenia related to hypersplenism and requiring SC who underwent PSE with N-butyl cyanoacrylate-methacryloxy sulfolane (NBCA-MS) Glubran®2 glue between February 2015 and September 2017 to correct thrombocytopenia and administer SC. Patients with renal insufficiency, allergy to contrast medium or life-expectancy <3 months were excluded from the study.

The study was approved by our Institutional Review Board and a waiver was granted for informed consent.

### *PSE procedure*

All PSE procedures were performed under intravenous sedation by 2 interventional radiologists with 6 and 12 years of experience, with the use of an Allura Xper FD 20 angio room system (Philips, Eindhoven, The Netherlands). Patients underwent diagnostic angiography under local anaesthesia by femoral approach through a 5.0-French sheath (Terumo, Tokyo, Japan). Selective cannulation of the splenic artery was then performed. Pre, per, and post angiography was carried out to identify left gastroepiploic artery, short gastric branches and pancreatic body and tail branches in order to avoid nontarget embolization. Following microcatheterization of branches supplying the splenic lower pole with a 2.7-Fr Progreat® microcatheter (Terumo, Tokyo, Japan), embolization was performed with a 1:5 ratio mixture of NBCA-MS (Glubran®2, GEM Srl, Viareggio, Italy) and Lipiodol® Ultra-Fluide (Guerbet, Aulnay-sous-Bois, France) to allow a distal embolization (Figure 1). The microcatheter was previously flushed with 5% dextrose solution. Splenic artery lower pole branches were preferentially occluded in order to minimize the occurrence of pleural effusion or subdiaphragmatic abscess. Then, injection of the mixture was slowly performed under fluoroscopy guidance to visualize the glue distribution until complete occlusion of the feeding branches (Figure 1). Postembolization 2D arteriogram and 3D Xper-CT imaging scan were used to estimate the percentage of splenic parenchyma occlusion. The embolization target was to obtain between 50% and 70% of infarcted spleen tissue, and this goal was estimated by the operator at the end of every procedure. A FemoSeal™ (Terumo) vascular closure device was systematically used at the femoral puncture site.

Regarding periprocedural medication, all patients



**Figure 1** 56-year-old man with hypersplenism-related thrombocytopenia requiring further systemic chemotherapy for stage IV colorectal carcinoma. (A) Contrast-enhanced computed tomography (CT) before partial splenic embolization (PSE) showing enlarged spleen. (B) Pre-embolization arteriogram with a 5-French catheter showing usual splenic arterial anatomy, with the splenic artery dividing into superior, middle and inferior terminal branches after splenic hilum. (C) Selective arteriogram obtained with 3-French microcatheter positioned in inferior terminal branch of the splenic artery shows appearance before embolization. (D) X-ray of the abdomen obtained after embolization of approximately 50% of spleen with a mixture of NBCA-MS (Glubran<sup>®</sup>2) glue and Lipiodol Ultra-Fluide in a ratio of 1:5 shows cast of liquid embolic agent within branches of inferior terminal branches of splenic artery. (E) Selective angiogram obtained with 3-French microcatheter positioned in middle terminal branch of the splenic artery shows appearance before embolization. (F) Immediate post-PSE arteriogram showing overall embolization of approximately 60 % of the splenic parenchyma. (G) Contrast-enhanced CT of the abdomen 2 weeks after PSE showing partial spleen necrosis (middle and lower pole), which accurately correlated with the post-PSE arteriogram. (H) Frontal CT reconstructions showing hyperdense material within spleen parenchyma which represents distribution of radiopaque liquid embolic agent within middle and inferior splenic artery branches.

**Table 1** Patient characteristics

Patient No.	Sex	Age (years)	Primary malignancy	Metastases
1	Male	66	Pancreatic adenocarcinoma	Liver Lung Peritoneum
2	Male	68	Colorectal cancer	Liver
3	Female	61	Colorectal cancer	Liver Lung
4	Female	53	Pancreatic adenocarcinoma	Peritoneum
5	Male	75	Gastric cancer	Liver Lung
6	Male	65	Hepatocellular carcinoma	Liver Peritoneum
7	Male	33	Colorectal cancer	Liver Lung
8	Male	51	Colorectal cancer	Liver Lung Peritoneum

received intravenous analgesia with 1 g of paracetamol during PSE and intravenous morphine if needed at the operator discretion. Patients were kept overnight for intravenous analgesia and antiemetic medications. They all took oral pain medication for 7 days and received empiric antibiotic coverage with amoxicilline 1 g per os/day for 10 days after PSE. Pneumococcal vaccine (Pneumovax, Merck) was systematically given before the procedure despite partial feature of splenic embolization.

### Data collection

In the framework of this study, each patient's demographic data, clinical presentation, etiology, laboratory values, and interventional data were collected. Information on length of hospital stay after the procedure, hospital readmissions, complications, and survival were obtained by review of the medical records. Duration of scopy and dose area product (DAP) were also recorded for each patient as radiation parameters during embolization procedure.

Pre- and post-procedural contrast-enhanced CT scan allowed to evaluate functional splenic volume with the

post-treatment software "AW Volume Share 5-Volume Viewer" (General Electric, Milwaukee, WI) by propagation of the manual contours of the total splenic volume. Splenic width and infarcted volumes were estimated by CT scan performed between 15 and 30 days after PSE, by manual contouring of necrotic and whole part of splenic parenchyma. The splenic infarction rate (%) was then calculated by using the following formula: splenic infarction rate (%) = (infarcted splenic volume/post-PSE splenic volume) × 100.

The primary and secondary endpoints of the present study included a platelet count increase >150×10<sup>9</sup>/L and the initiation of SC, respectively. The arbitrary platelet count of 150×10<sup>9</sup>/L was chosen as a value that was sufficiently above the minimum thresholds commonly used in clinical practice for the safe administration of SC that impact bone marrow function (16-19). Periprocedural laboratory values were recorded. Platelet, white blood cell and red blood cell counts was monitored immediately before PSE and at days 10, 20 and 30 after PSE.

All adverse events were recorded and classified as minor or major complications according to the Society of Interventional Radiology classification system.

### Statistical analysis

Values are presented as means for quantitative variables and as percentages for qualitative variables. Summary statistics were calculated for platelet count as well as white blood cell and red blood cell counts. Changes in blood cell counts over time were analyzed with a linear mixed model according to time, taking into account potential staggering variables. A P value of ≤0.05 was considered significant. Statistical analyses were performed using STATA software (version 12.0, STATA corp., College Station, Texas, USA).

## Results

### Patient characteristics

Between February 2015 and September 2017, 8 patients (6 males, 2 females; median age, 59 years; range, 33–75 years) underwent PSE for the purpose of correcting thrombocytopenia to administer optimally dosed SC. All patients had malignancies arising from the gastrointestinal tract at the time of PSE (Table 1). Primary malignancies included colorectal cancer (n=4), pancreatic adenocarcinoma (n=2), hepatocellular carcinoma (n=1), and gastric cancer

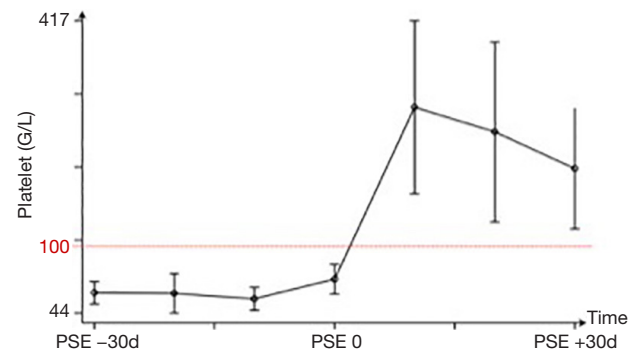


**Table 2** PSE outcomes and periprocedural data

Variable	No. (%) or [range]
Immediate technical success	8/8 (100.0)
Primary endpoint	7/7 (100.0)
Secondary endpoint	7/7 (100.0)
Mean duration of scopy (min)	24 [14–36]
Mean DAP (Gy*cm <sup>2</sup> )	407 [179.7–624.7]
Mean splenic width (cm)	
Pre-PSE	156 [126–212]
Post-PSE	154 [129–210]
Mean splenic volume (cm <sup>3</sup> )	
Pre-PSE	802 [397–1,727]
Post-PSE	856 [465–2,114]
Mean splenic embolized volume (cm <sup>3</sup> )	501 [99–1,314]
Mean splenic infarction percentage	55.1 [21.3–69.9]
Mean platelet count (×10 <sup>9</sup> /L)	
Immediately before PSE	74 [62–83]
10 days after PSE	272 [161–417]
20 days after PSE	239 [120–381]
30 days after PSE	195 [117–273]
Mean hospital discharge (days)	3.4 [2–6]
Readmission within 30 days of PSE	0 (0)
Complications	5 (62.5)
Minor	5 (62.5)
Major	0 (0)
Postembolization syndrome	5 (62.5)
Moderate	5 (62.5)
Severe	0 (0)
Non-target glue embolization	0 (0)
One-month mortality rate	1/8 (12.5)
Related to the procedure	0/8 (0)
Unrelated to the procedure	1/8 (12.5)
Mean overall survival at follow-up (months)	7.9 [0.3–10.4]

PSE, partial splenic embolization; DAP, dose area product.

(n=1). Hepatic and lung metastases were present in 7 and 5 patients, respectively. Hypersplenism was the suspected cause of thrombocytopenia in all patients based on clinical



**Figure 2** Platelet count by time. The mean platelet count significantly increased after PSE ( $P<0.05$ ) and peaked at  $272 \times 10^9/\text{L}$  [range,  $(161\text{--}417) \times 10^9/\text{L}$ ] 10 days after PSE. Mean platelet count at days 20 and 30 post-PSE were  $239 \times 10^9/\text{L}$  [range,  $(120\text{--}381) \times 10^9/\text{L}$ ] and  $195 \times 10^9/\text{L}$  [range,  $(117\text{--}273) \times 10^9/\text{L}$ ], respectively.

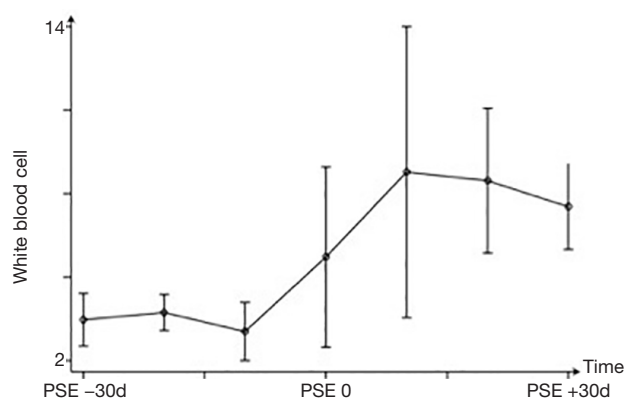
and radiological assessment. Furthermore, pre-procedural CT scan imaging revealed a mean splenic width of 156 mm (range, 126–212 mm) for the patient cohort, which is consistent with splenomegaly. Total pre-procedural splenic volume was estimated at 802 cm<sup>3</sup> (range, 397–1,727 cm<sup>3</sup>) (Table 2).

### PSE outcomes

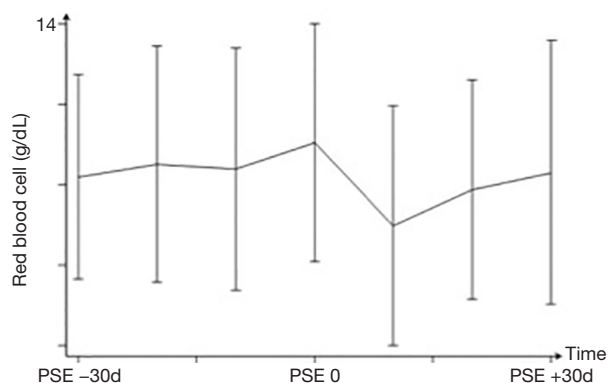
PSE was technically successful in all patients (100%). The mean duration of scopy was 24 min (range, 14–36 min). Mean DAP was 407 Gy\*cm<sup>2</sup> (range, 179.7–624.7 Gy\*cm<sup>2</sup>). CT scan was performed at 19 days on average after PSE (range, 15–30 day). Mean post-PSE splenic width and volume were 154 mm (range, 129–210 mm) and 856 cm<sup>3</sup> (range, 465–2,114 cm<sup>3</sup>), respectively. Mean post-PSE splenic infarction was 55.1% (range, 21.3–69.9%).

The mean platelet count immediately before PSE was  $74 \times 10^9/\text{L}$  [range,  $(62\text{--}83) \times 10^9/\text{L}$ ], confirming low platelet count for all patients prior to PSE. For procedures with available laboratory follow-up, primary endpoint was achieved in 7 (100%) of 7 patients with one-single procedure. The mean platelet count significantly increased after PSE ( $P<0.05$ ) and peaked at  $272 \times 10^9/\text{L}$  [range,  $(161\text{--}417) \times 10^9/\text{L}$ ] 10 days after PSE. Mean platelet count at days 20 and 30 post-PSE were  $239 \times 10^9/\text{L}$  [range,  $(120\text{--}381) \times 10^9/\text{L}$ ] and  $195 \times 10^9/\text{L}$  [range,  $(117\text{--}273) \times 10^9/\text{L}$ ], respectively (Figure 2).

After PSE, the same trend of changes was observed for white blood cell count but with no significant peak level (Figure 3). Red blood cell count showed no significant



**Figure 3** White blood cell count by time. The mean white blood cell count increased after PSE ( $P>0.05$ ) and peaked 10 days after PSE but not significantly.



**Figure 4** Red blood cell count by time. The mean red blood cell count decreased after PSE but not significantly over time.

changes over time, even after PSE (Figure 4).

The secondary endpoint of SC administration was achieved in all patients with adequate follow-up (7 of 7 patients) within 30 days after PSE. No repeat PSE was performed. Mean hospital discharge was 3.3 days after PSE (range, 2–6 days). No readmission within 30 days of PSE occurred. PSE outcomes are summarized in Table 2.

### Complications

No non-target glue embolization occurred. No puncture site hematoma was noted. No major complication or grade 3 or above adverse events were reported. No severe postembolization syndrome occurred. Five (62.5%) patients experienced transient and moderate postembolization syndrome. Four patients (50%) referred low to moderate

abdominal pain, 3 patients (37.5%) had low-grade fever, and 3 patients (37.5%) had nausea. The mean overall survival was 7.9 months (range, 0.3–10.4 months) among the 8 patients after PSE. One patient with pancreatic adenocarcinoma died within 10 days of PSE because of disease progression and had no biological/radiological follow-up (Table 2).

### Discussion

All patients of the present study had documented splenomegaly based on imaging criteria and had hypersplenism-induced thrombocytopenia secondary to chemotherapy-associated hepatic injury. The primary and secondary endpoints included a platelet count increase  $>150 \times 10^9/L$  and the initiation of SC, respectively. For procedures with available laboratory follow-up, primary endpoint was achieved in 7 (100%) of 7 patients with one-single procedure. The mean platelet count significantly increased after PSE ( $P<0.05$ ) and peaked at  $272 \times 10^9/L$  [range, (161–417)  $\times 10^9/L$ ] 10 days after PSE. The secondary endpoint of SC administration was achieved in all patients with adequate follow-up (7 of 7 patients) within 30 days after PSE.

PSE has become a good and efficient alternative to splenectomy for the treatment of refractory hypersplenism-related thrombocytopenia in oncologic patients requiring SC (2–7). Such patients are often late stage and poor candidates for splenectomy, requiring palliative treatment (8,9). Successful management of their thrombocytopenia is essential to give them access to further chemotherapy. PSE is considered relatively safe (16–18). Postembolization syndrome (PES), consisting of abdominal pain, low-grade fever and nausea is a common expected side effect of embolization of a solid organ and was encountered moderately in 62.5% of patients in the present study. No severe PES was noted here. However, small numbers of major complications including splenic abscess or rupture, reactionary pleural effusion and pneumonia have been reported. None of the patients in the current series developed splenic abscess. The rate of severe complications varies in relation to the volume of splenic infarction. If it is more than 70% of the splenic volume, severe complications develop in 50% compared to 8.8% if the infarctus is between 50% and 70%. Thus, it is admitted that infarctus should be between 50% and 70%, to ensure effective management of hypersplenism and reduce severe complications (4,5,16–18). In our study, most of the patients had a 50–70% infarction

area with no major complications. In 100% of our cases, patients were kept overnight for symptomatic treatment. This not consistent with more recent publications in which PSE was often times conducted as an outpatient procedure (19). However, even if the risk-benefit ratio supports PSE in these poor patients who require palliative treatment, the risk of severe complications makes preferable keeping them overnight if symptomatic treatment is needed. On the same way, although no recommendation exists regarding specific precautions against infection with PSE such as pneumococcal vaccination or prophylactic antibiotics, all patients in the present study were treated with these two options to minimize the risk of infectious complications, as those we can see after splenectomy, by analogy

SC treatments, which involve oxaliplatin, have been linked to the appearance of distinctive liver lesions, such as hepatic sinusoids blockade, sclerosis of the perisinusoidal space, and veno-occlusive disease, affecting the normal hepatic parenchyma and occasioning portal hypertension (5,19-23). Increases in spleen size, platelets splenic sequestration, and development of thrombocytopenia are surrogates of this toxicity. In our study, drug toxicity was identified as the main indirect cause of thrombocytopenia in all patients.

The arbitrary platelet count of  $150 \times 10^9/\text{L}$  was chosen as a value that was sufficiently above the minimum thresholds commonly used in clinical practice for the safe administration of SC that impact bone marrow function. A successful platelet increase above this threshold value was achieved in 100% of patients (7). In addition, the mean peak platelet value of  $272 \times 10^9/\text{L}$  achieved in the current study is comparable to that achieved in most of other reported series (7,11,19,20). Subsequently, SC was successfully administered after the procedure in all patients with adequate follow-up.

The choice of the best embolic agent is still controversial. To our knowledge, there is no series in the literature reporting results of PSE in the treatment of hypersplenism-related thrombocytopenia with the use of NBCA-MS Glubran®2 glue. As far as we are aware, this is the first report reporting the use of glue. Uncharged microparticles such as microspheres are the most commonly used for embolization in previous reports but the risk of ischemic complication may be higher than that with proximal agents such as coils or plugs (12-14). Furthermore, it might be difficult to determine the appropriate size of particles to be used based on angiography. Mechanical agents result in occlusion of the splenic artery but with

minimal change in the splenic parenchyma unless the collateral network is affected. The mechanism of action of coils and plugs is entirely occlusive and their effect is equivalent to surgical ligation of the main splenic artery. One disadvantage of these mechanical embolic agents is that they are not as effective in the presence of collateral vessels, which may lead to recanalization. The main goal of PSE is to superselectively destroy part of the spleen. The intra-parenchymatous branches of the splenic artery must, therefore, be occluded as distally as possible. Embolic agents causing distal embolization such as microparticles or resorbable gelatin may therefore be used (13,14). According to Zhu *et al.*, microparticles are more effective than absorbable gelatin in increasing the platelet count, with no difference in the rate of complications. However, the procedure can be time-consuming with microparticles. NBCA-MS (Glubran®2) was chosen in this study for embolization. Glubran®2 is a well-known surgical glue in which NBCA is combined with another monomer, methacryloxy sulfolane (MS), to produce a more pliable and stable polymer whose milder exothermic reaction (45 °C) results in less inflammation and histotoxicity than Histoacryl® or Trufill®, which are respectively not allowed for endovascular purpose and not available in Europe (15). Cyanoacrylate glues in general, and NBCA-MS Glubran®2 in particular, have the advantage of offering permanent embolization, independently of coagulation disorders. Another advantage is that the use of glue for PSE is fast and may lead to shorter duration of scopy, lower DAP and less radiation. Furthermore, embolization with NBCA-MS Glubran®2 is cost-effective in comparison with other embolic agents (24). One cc, which is the standard dose used for each patient in our series, is 3 times cheaper than any detachable coil, plug or vial of microparticles. One technical aspect is that cyanoacrylate should be mixed with Lipiodol to make the mixture radiopaque, and released under fluoroscopic control. The mixture with Lipiodol also modulates the polymerization rate. In all of our patients, we used a glue-Lipiodol ratio of 1:5, thus achieving distal intraparenchymal embolization. Indeed, the goal here is to obtain a distal embolization. For this purpose, it is needed to use a higher ratio than usual (1:3) in order to delay the polymerization of the glue in contact with blood and allow the mixture reach the distal parenchymal vascular bed before polymerization (15). Cyanoacrylate is more viscous than microparticles (24-27). The possibility of significant ischemic complications is therefore unlikely. The last advantage of the glue/lipiodol mixture is the high

radiopacity. It allows to accurately check the distribution of the embolic agent into the splenic parenchyma during the angiography. It might be very useful in achieving a more reliable analysis of the embolized spleen, especially on per-procedural cone-beam CT imaging or during CT scan follow-up, even without injection of contrast medium (6,15,24). Glue embolic agents however present some drawbacks. Possible complications of cyanoacrylate PSE are glue migration in non-target vessels and a glued catheter (15,25,26). We had no such complications in our series because the glue embolization was performed by radiologists with considerable experience in the use of tissue adhesives.

Our study has some limitations. First, this is a single-center study with a small number of patients. Second, there is no control group. Comparing PSE with the use of other embolic materials might help determine the best embolic agent. Furthermore, a control group aiming for a smaller splenic infarcted area to determine the best embolization fraction could be of interest. Third, ideal criteria and perfect timing for the selection of patients should be well established to determine eligibility for the procedure. As for last limitation, this includes short follow-up time.

In conclusion, this study demonstrates that PSE with NBCA-MS Glubran®2 glue is safe and effective in the management of thrombocytopenia related to hypersplenism in cancer patients. It allows sufficient platelet count improvement for administration of SC and confirms that aiming for a 50–70% infarcted area may be sufficient to achieve success without any complications. This finding, combined with the lack of severe PES after PSE, makes it an excellent therapeutic option in the management of hypersplenism-related thrombocytopenia, allowing patients to receive SC with minimal procedure-related morbidity. Future larger studies are needed to confirm the safety and efficacy of this intervention with glue. If so, cyanoacrylate glue may prove to be the preferable agent for PSE.

## Acknowledgements

None.

## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Ethical Statement:* This retrospective study was performed in

compliance with the requirements of the institutional review board and approved by the institution ethical committee. Informed consent was waived.

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