

## Partial Splenic Embolization for the Treatment of Thrombocytopenia in Cancer Patients

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### 1. Abstract

Thrombocytopenia is a common sequela of chemotherapy treatment of many non-hematologic malignancies. Severe thrombocytopenia may necessitate halting chemotherapy or lead to hemorrhagic complications that impact patient morbidity and mortality. Partial Splenic Embolization (PSE) has been shown to be effective at improving platelet counts in appropriately selected patients and allowing for the resumption of chemotherapy. Many patients develop a sustained response to PSE, while thrombocytopenia recurs in others. Post-embolization syndrome is the most common complication of PSE and is characterized by fever, pain and nausea/vomiting. The incidence of complications increases with the percentage of splenic volume embolized. The purpose of this review is to summarize the current literature regarding the use of PSE to reduce thrombocytopenia in cancer patients and to highlight techniques and complications.

### Key Points

- Partial splenic embolization is an effective procedure in the treatment of thrombocytopenia in cancer patients, allowing the resumption of chemotherapy in the majority of patients.
- A wide variety of techniques are effective in performing partial splenic embolization procedures.
- Post-embolization syndrome symptoms including abdominal pain, fever, and nausea are common after partial splenic embolization in cancer patients.
- Partial splenic embolization is a safe procedure with a low incidence of major complications.

### 2. Introduction

Cancer patients with hypersplenism-related thrombocytopenia have limited options. Platelet transfusions are often ineffective at maintaining sufficient levels to allow for continued treatment and delays in therapy are not uncommon [1, 2]. Cessation or dose reduction of chemotherapy may be detrimental to the long-term outcome of patients with malignancy which is otherwise responsive to chemotherapy. Although total splenectomy may be effective, the operative risks are often prohibitive in this fragile patient population [3]. Two thrombopoietin growth factors, eltrombopag and romiplostim, are under investigation for chemotherapy-induced thrombocytopenia, but neither have been approved to date [4].

Partial splenic embolization (PSE) for the treatment of hypersplenism was first described in 1979 by Spigos et al using absorbable gelatin sponge suspended in an antibiotic solution of penicillin G and gentamicin [5]. In 1982 Lokich and Costello described the use of splenic embolization in two patients with severe thrombocytopenia precluding further treatment with chemotherapy [6]. Since that time, PSE has been reported in many studies in patients with thrombocytopenia related to cirrhosis and hypersplenism secondary to portal hypertension. Several studies reporting outcomes of PSE in series of cancer patients with thrombocytopenia have also been reported. The purpose of this review is to summarize the current literature of PSE and its utility in cancer patients with thrombocytopenia.

### 3. Etiology of Hypersplenism-Associated Thrombocytopenia

The spleen is a complex organ which can be conceptually divided into

two compartments: the blood-rich red pulp and the lymphoid containing white pulp. The red pulp of the spleen serves an important role in the filtration of cellular debris, pathogens and aging erythrocytes from the blood by abundant macrophages [7]. The white pulp of the spleen provides an organized lymphoid compartment, which is critical to antibacterial and antifungal immune responses within the bloodstream[7]. Although the pathogenesis of thrombocytopenia in patients with portal hypertension is multifactorial, platelet sequestration secondary to splenomegaly has been implicated as a contributing factor to the reduction of circulating red blood cells, leukocytes as well as platelets [8].

Thrombocytopenia is frequently encountered in patients receiving chemotherapy for the treatment of solid organ malignancies, particularly in those receiving regimens with oxaliplatin [9, 10]. Oxaliplatin, which is commonly utilized in the treatment of colorectal cancer as well as other malignancies of the ovary, breast and liver, is associated with the development of thrombocytopenia in up to 70% of patients [11]. Chemotherapy-induced bone marrow suppression is often implicated as the primary cause of thrombocytopenia. However, hepatic sinusoidal injury leading to portal hypertension and splenic sequestration as well as a reduction in thrombopoietin production is increasingly recognized [12].

#### **4. Clinical Studies**

The majority of published series describing PSE involve cirrhotic patients with thrombocytopenia. An electronic search of PubMed (Medline) yielded a total of seven publications describing experience with partial splenic embolization for the treatment of thrombocytopenia in cancer patients, the majority of which were retrospective reviews (Table 1). The search terms used included “splenic embolization”, “thrombocytopenia” and “cancer.” All series including greater than three patients and published in the last 30 years were reviewed and included for analysis. Mean platelet volume prior to PSE and after PSE was recorded if provided. Ability to restart chemotherapy after PSE and days to re-initiation of chemotherapy was also evaluated if provided. The frequency of post-embolization syndrome, mean hospitalization days and incidence of major complications were also evaluated if available.

#### **5. Technique**

Partial splenic embolization may be performed via transfemoral or transradial artery access [13, 14]. Transradial artery access for interventions below the diaphragm has become increasingly popular as it does not require bedrest, is associated with reduced operator radiation exposure and increased patient satisfaction when compared to transfemoral artery access [15, 16]. Furthermore, transradial artery access for visceral angiography has been shown to be safe in patients with thrombocytopenia and may reduce the need for platelet transfusion prior to intervention [17]. The celiac artery may be easily catheterized with a wide variety of 4- or 5-French catheters. Celiac angiography allows for evaluation of the splenic artery as well as visceral anastomoses, which may provide important collateral supply

to the spleen including the dorsal pancreatic, pancreatica magna, left gastric and gastroepiploic arteries.

Spigos et al first reported partial splenic embolization in the treatment of hypersplenism using absorbable gelatin sponge suspended in an antibiotic solution of penicillin G and gentamicin [11]. Approximately 60-90% of the splenic parenchyma was embolized in the six cases reported by Spigos et al. Although angiographic techniques have evolved with improved imaging technology and a greater availability of catheters and embolic materials, the endpoints and method of embolization in contemporary practices remains similar. We performed a review of the English language literature for PSE in the treatment of thrombocytopenia in cancer patients and included all retrospective and prospective series (Table 1).

PSE is typically performed using particulates such as absorbable gelatin sponge or microspheres. The percentage of splenic parenchyma embolized is typically subjectively assessed by the operator using intermittent digital subtraction angiography. Hill et al and Kauffman et al, both retrospective reviews, reported the use of gelatin sponge suspended in gentamicin solution for embolization, a technique that accounts for the majority of patients reported [18, 19]. Kauffman et al reported a wider range of percentage splenic parenchyma embolized of 25-80%, while Hill et al reported a target of 50-75% as determined by intermittent digital subtraction angiography. Luz et al presents the only prospective series of cancer patients treated with PSE for thrombocytopenia in which embolization was performed using 100-300-micron polyvinyl alcohol microspheres mixed with gentamicin targeting 50-70% of the splenic parenchyma [20]. Passhak et al reported embolization using particles ranging in size from 300 to 700 microns targeting 50% of the splenic parenchyma [21]. Similarly Kis et al reported embolization using 300-500-micron tris-acryl gelatin microspheres targeting a 50-60% of splenic parenchyma [22]. As in PSE performed in patients with cirrhosis and hypersplenism, distal splenic artery embolization with selective targeting of lower pole branches is preferred to reduce risk of significant post-procedural pain, subdiaphragmatic abscess and thoracic complications such as lung atelectasis and pleural effusion [23]. While embolizations reported by Luz et al and Kis et al were performed specifically targeting lower pole branches of the spleen, Passhak et al reported embolization was performed more proximally from the splenic artery just distal to the origin of the major pancreatic branches [20-22]. Alternatives to particulate embolization for use in PSE in cancer patients have also been reported. Bhatia et al retrospectively reviewed a series of 13 patients with chemotherapy-induced thrombocytopenia treated with proximal splenic artery occlusion using platinum coils without particulate embolization [24]. Loffroy et al retrospectively reviewed a series of 8 patients with chemotherapy-induced thrombocytopenia and hypersplenism treated with PSE using a liquid glue embolic agent, N-butyl cyanoacrylate-methacryloxy sulfolane, mixed with ethiodol [25]. In these patients, occlusion of splenic artery lower pole branches was achieved after microcatheter selection of appropriate branches.

**Table 1:** Partial splenic embolization study demographics

Author/Year	Country	Study type	Number of patients	Extent of splenic ischemia targeted	Emolic used for PSE	Mean platelet count prior to PSE
Bhatia SS/ 2015	USA	Retrospective review	13	N/A	Platinum coils	88 x 10 <sup>9</sup> /L
Hill A/ 2020	USA	Retrospective review	98	50-75%	Gelatin sponge	61 x 10 <sup>9</sup> /L
Kauffman CR / 2008	USA	Retrospective review	28	25-80%	Gelatin sponge or microspheres	81 x 10 <sup>9</sup> /L
Kis B / 2020	USA	Retroseptive	35	50-60%	300-500 um tris-acryl gelatin microspheres	65.7 x 10 <sup>9</sup> /L
Loffroy R/ 2019	France	Retrospective review	8	50-70%	N-butyl cyanoacrylate-methacryloxy sulfolane glue and ethiodol	74 x 10 <sup>9</sup> /L
Luz JHM/ 2016	Brazil	Nonrandomized prospective study	33	50-70%	100-300 um polyvinyl alcohol microspheres	69 x 10 <sup>9</sup> /L
Passhak M/ 2018	Israel	Retrospective review	10	50%	300-700 um microspheres	64.6 x 10 <sup>9</sup> /L

## 6. Clinical Outcomes

Clinical outcomes from available studies are summarized in Table 2. Comparison of outcomes between studies is limited as studies reported on a variety of measurable outcomes. All studies reported a mean platelet count prior to embolization; however, one study did not report mean platelet counts after PSE. Mean platelet count prior to PSE ranged from 64.6 x 10<sup>9</sup>/L to 81 x 10<sup>9</sup>/L, while mean reported platelet count after the procedure ranged from 188 x 10<sup>9</sup>/L to 293 x 10<sup>9</sup>/L after PSE. The mean pooled platelet count prior to PSE was 73 x 10<sup>9</sup>/L, while the platelet count after PSE was 230 x 10<sup>9</sup>/L, with

an increase of 158 x 10<sup>9</sup>/L in mean platelet count across all studies which reported an average platelet count after embolization. Instead of reporting mean platelet counts after embolization, Hill et al stratified patients based on degree of response, ranging from complete responders who achieved platelet counts greater than 100 x 10<sup>9</sup>/L and did not develop recurrent thrombocytopenia below this threshold, partial responders who achieved platelet counts above this threshold transiently, and non-responders who were unable to achieve platelet counts above 100 x 10<sup>9</sup>/L<sup>19</sup>. Three patients in that study had PSE to increase platelet counts prior to surgery. Re-initiation of chemotherapy was successfully achieved after PSE in 97% of the remaining patients in that study.

**Table 2:** Partial splenic embolization study outcomes and complications

Author/Year	Mean peak platelet count after PSE	Frequency of post-embolization syndrome	Major complications	Mean hospitalization days	Restarted chemotherapy after PSE*	Days to chemotherapy re-initiation after PSE
Bhatia SS/ 2015	209 x 10 <sup>9</sup> /L	8%	0%	0.1	100%	22
Hill A/ 2020	Not reported	Not reported	8%	Not reported	97%	25
Kauffman CR / 2008	293 x 10 <sup>9</sup> /L	100%	Not reported	4.5	96%	32
Kis B / 2020	221 x 10 <sup>9</sup> /L	92%	44%	2.6	Not reported	Not reported
Loffroy R/ 2019	272 x 10 <sup>9</sup> /L	100%	0%	1	100%	Not reported
Luz JHM/ 2016	188 x 10 <sup>9</sup> /L	Not reported	0%	Not reported	100%	14
Passhak M/ 2018	224 x 10 <sup>9</sup> /L	10%	0%	2.5	100%	18

\*The percentage of patients for whom the goal was to resume chemotherapy is reported.

Furthermore, chemotherapy was successfully resumed in 96-100% of patients after PSE across all studies in whom the goal was to resume treatment. Mean time to re-initiation of chemotherapy after PSE ranged from 14 to 32 days. The mean pooled time to resumption of chemotherapy across all studies was 23.5 days. The overall pooled success rate in resumption of chemotherapy across all studies

was 97.7% in patients in whom PSE was performed to allow for resumption of chemotherapy. Two studies did not report the ability to resume chemotherapy after PSE and primarily discussed the impact of PSE on mean platelet count over time. The overall success rate of the procedure at achieving the desired clinical outcome was similar across the different studies reviewed.

PSE resulted in a durable improvement in platelet count in the majority of patients in studies where the long-term impact on thrombocytopenia was evaluated. Bhatia et al reported a mean platelet count of  $152 \times 10^9/\text{L}$  at a mean long-term follow-up of 9.2 months, increased from a mean pre-PSE platelet count of  $88 \times 10^9/\text{L}$ .<sup>24</sup> Hill et al reported that 64% of patients who survived greater than 12 months after PSE maintained a platelet count greater than  $100 \times 10^9/\text{L}$ , increased from an average pre-PAE platelet count of  $74 \times 10^9/\text{L}$  in that subset of patients.<sup>19</sup> Kis et al reported a mean platelet count of  $174 \times 10^9/\text{L}$  in patients who survived greater than 12 months after PSE.<sup>22</sup>

## 7. Peri-Procedural Care

The use of pre-procedural or post-procedural antibiotics for patients undergoing PSE varies by institution and a variety of protocols are reported. Practice parameters endorsed by the Society of Interventional Radiology, the Cardiovascular and Interventional Radiological Society of Europe and the Canadian Society of Interventional Radiology, recommend routine antibiotic prophylaxis if greater than 70% of splenic parenchyma is embolized, but provide no expert consensus on the first-choice antibiotic regimen.<sup>26</sup> A variety of suggested regimens are suggested, many of which recommend post-procedure intravenous or oral antibiotics for five days after the procedure.<sup>[26]</sup>

Kauffman et al and Hill et al described the use of absorbable gelatin sponge mixed with gentamicin antibiotic solution similar to the technique described in the original PSE series reported by Spigos et al [11, 18, 19]. Pre-procedure and post-procedure antibiotics were not routinely administered. All patients treated by Passhak et al received pre-procedure intravenous antibiotics, but were not routinely prescribed post-procedure antibiotics.<sup>[21]</sup> Patients treated by Luz et al and Loffroy et al were routinely prescribed post-procedure oral antibiotics for 7-10 days [20, 25]. Patients treated by Kis et al also routinely received intravenous antibiotics and were transitioned to oral antibiotics upon discharge for a total of 7 days [22].

Vaccination against encapsulated pathogens such as Pneumococcus, Haemophilus influenza and Meningococcus is also variable. Bhatia et al and Loffroy et al reported pre-procedural vaccination for all patients, while Hill et al reported vaccination at time of discharge after PSE [19, 24, 25]. Kis et al reported pre-procedural pneumococcal vaccination for all non-immunized patients [22]. The need for prophylactic vaccination after splenic artery embolization is unknown and was not routinely practiced in several series of patients treated with splenic embolization for other indications such as trauma, thrombocytopenia due to cirrhosis, aneurysm and gastric variceal hemorrhage [27-30].

Patients are commonly admitted after PSE for overnight observation and pain management. In patients treated with proximal splenic artery occlusion using platinum coils, all but one out of 13 patients were successfully discharged home the day of the procedure.<sup>[24]</sup> Although this low incidence of significant post-procedural pain after PSE is desirable, coil embolization may preclude future splenic

embolization procedures if thrombocytopenia recurs. Length of reported hospitalization in patients treated with particulate splenic embolization ranged from 1 day to 23 days with mean hospitalization varying from 1 day to 4.5 days (Table 2).

## 8. Complications

Post-embolization syndrome, which consists of fever, nausea and/or left upper quadrant pain, was commonly reported after PSE in cancer patients, occurring in up to 100% of patients in some series [18, 25]. Even in patients treated with proximal splenic artery coil embolization who were routinely discharged home the day of the procedure, post-procedure abdominal pain was reported in 46% of cases [24]. Although Passhak et al reported only one case of post-embolization syndrome (fever and abdominal pain) in their series of 10 patients, post-procedure abdominal pain occurred in all patients, reflecting the varied interpretation in the definition of post-embolization syndrome by different operators and authors [21]. Kis et al reported varying degrees of abdominal pain in 92% of all patients who underwent PSE.<sup>22</sup> Moderate and severe pain was less frequent in patients treated with celiac plexus neurolysis (18.5% vs 92%) [22]. Other complications were infrequent including superior mesenteric vein thrombosis in one patient with prolonged hospitalization, focal pancreatitis, asymptomatic non-occlusive splenoportal thrombosis, splenic subcapsular hematoma, pneumonia and transient elevations in serum bilirubin [18, 19, 22]. Death was reported in three patients who developed sepsis after PSE [19, 22]. One patient died after development of an intracranial hemorrhage, which occurred within 30 days of PSE.<sup>22</sup> No splenic abscesses were reported in any of the series reporting PSE in cancer patients. Overall, the incidence of major complications reported varies greatly, likely reflecting variations in what constitutes a major complication by different authors.

Other complications encountered after PSE for other indications such as trauma and thrombocytopenia in cirrhosis include pleural effusion, abscess, variceal bleeding, portal vein thrombosis and even death [30, 31]. Major complications are more frequently encountered in patients with greater than 70% embolization of splenic parenchyma [31, 32].

## 9. Future Directions

Although PSE has been shown to be a safe and effective procedure to address thrombocytopenia in patients with cancer, there is still wide variability in how it is performed. Additional prospective studies assessing safety and efficacy of different types and sizes of embolic materials would be valuable. There is also wide variability in the percentage of splenic parenchyma embolized as well as the method by which this is calculated. A standardized method of calculating percentage of parenchyma embolized would be useful to incorporate into future studies; this should be feasible in most modern angiography suites capable of performing cone-beam CT [33]. Treatment algorithms are also widely disparate in the current literature. Although the goal platelet count may differ from patient to patient, standardized thresholds for determining treatment failure or success would be

helpful in developing clinical algorithms as well as guiding decisions regarding follow-up procedures.

## 10. Conclusions

PSE is an effective and safe procedure in thrombocytopenic cancer patients. Splenic parenchyma infarction is most commonly achieved using particulates such as absorbable gelatin sponge or microspheres. However, embolization of lower pole splenic branches using glue and proximal coil embolization of the splenic artery have been shown to be effective and safe in a small number of patients. In cancer patients with thrombocytopenia, PSE offers an effective alternative to splenectomy in a fragile population where surgery is often avoided. Most patients (96-100%) are able to resume chemotherapy two to four weeks after PSE.

Although PSE should be considered safe, most patients will experience some symptoms of post-embolization syndrome including pain, fever, or nausea. Major complications are rare in most reported series; however, readmission for persistent post-embolization syndrome, serious infection and even death have all been reported. To minimize the risk of PSE-related complications, the target for volume of splenic parenchyma embolized should be below 70%.

In appropriately selected thrombocytopenic cancer patients, PSE is an effective and safe procedure, which will reliably raise platelet counts in patients with hypersplenism and allow for resumption of chemotherapy.

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