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A Case Study Using Papaya Leaf Extract to Reverse Chemotherapy-Induced Thrombocytopenia in a GBM Patient

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Abstract

Chemotherapy-induced thrombocytopenia (CIT) is a critical condition in which platelet counts are abnormally reduced following the administration of chemotherapeutic compounds. CIT poses a treatment conundrum to clinicians given the increased risk of spontaneous bleeding, obstacles to surgical management of tumors, and exclusion from clinical trials. Treatment of CIT involves the removal of the offending agent combined with platelet infusion or thrombopoietin agonist treatment. However, due to the autoimmune and infection risks associated with infusions, this treatment is only reserved for patients with critically low platelet counts. One potential solution for patients in the mid to low platelet count range is *Carica papaya* leaf extract (CPLE). In this case, we report the novel use of CPLE as a method of bolstering platelet counts in a patient presenting with CIT. The patient was initiated on CPLE therapy consisting of 1 tablespoon twice daily with meals. Following CPLE treatment, the patient's platelet counts rebounded from less than 10,000/μL to 113,000/μL. This clinical vignette supports the use of CPLE in the clinical context of CIT when thrombopoietin agonists are not a viable option. The potential benefits of CPLE as a method for increasing platelet count deserve further exploration, especially as a treatment option for refractory patients or those ill-suited for other traditional thrombocytopenia therapies.

Keywords

Carica papaya, papaya leaf extract, chemotherapy-induced thrombocytopenia, platelets, temozolomide, Glioblastoma multiforme

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Background

Thrombocytopenia is described as a hematologic incidence of low platelet counts below 150,000/μL.[1] When severe, this phenomenon can significantly increase the risk of subsequent hemorrhagic events for affected patients.[1] Chemotherapy-induced thrombocytopenia (CIT) is a common cause of thrombocytopenia as it affects nearly 300,000 cancer patients/year.[2] CIT affects ~10% to 38% of solid tumor cancer patients and ~40% to 68% of patients with hematologic malignancies.[3] CIT can result from treatment with cyclophosphamide or other alkylating agents.[2] These agents can negatively affect pluripotent stem cells and megakaryocyte progenitors, the precursors from which platelets proliferate, in bone marrow.[2] Thrombocytopenia resulting from chemotherapy varies by treatment regimen; however, there is an 82% incidence of CIT in patients who receive carboplatin monotherapy.[3] Similar to carboplatin, temozolomide (TMZ) is an alkylating agent; thus, we can expect similar thrombocytopenic side effects. Especially in combination with radiotherapy, temozolomide has the potential to cause thrombocytopenia in newly diagnosed high-grade glioma patients. Approximately 15% to 20% of those patients will experience subsequent, persistent thrombocytopenia, which puts them at an increased risk for bleeding, ineligibility for clinical trials, and cessation of chemotherapeutic regimes.[4]

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The potential active constituents of *Carica papaya* leaf extract (CPLE) have been detailed thoroughly in other publications; however, a few key constituents play a role in platelet recovery.[5] One study investigated the hematologic effects of CPLE in a murine model and reported significant increases in both platelet count and red blood cell counts after mice received fresh CPLE.[6] Subsequently, the use of CPLE was evaluated in dengue fever patients who often experience thrombocytopenia. The study group was treated with papaya leaf extract via capsule, which resulted in higher overall platelet counts, decreased platelet transfusion requirements, and shorter hospital stays.[7] Additional studies have shown comparable results with papaya leaf juice.[8] Due to the reported success of CPLE in addressing thrombocytopenia in animal models and dengue fever patients, its use was adopted for the treatment of CIT. One study found that patients who received CPLE had increased platelet counts, as well as improvements in other hematological parameters.[2] CPLE has also been proven to reduce CIT-related delays in chemotherapy administration.[9] Additional studies on post-chemotherapy populations have mirrored the results of these studies and have found no treatment-related adverse events; however, a recent review has reported that the most common side effect of CPLE use is minor gastrointestinal disturbance.[10,11] Recently, a case report of a neonate with persistent refractory thrombocytopenia concluded that CPLE treatment may even be applicable in this population.[12]

Case Presentation

A 43-year-old man presented to the emergency room with a right-sided facial droop, right upper extremity weakness, and generalized fatigue. Magnetic resonance imaging (MRI) of his brain revealed an expansile left thalamic FLAIR signal abnormality with extension into the left mesial temporal structures and rostral brainstem bilaterally. Intermittent small regions of enhancement measuring 3 to 4 mm were noted, concerning for high-grade glioma (Figure 1A-E). A stereotactic biopsy was performed which confirmed glioblastoma multiforme (GBM). As such, the patient was treated with concurrent chemoradiation per the Stupp protocol,[13] and his baseline platelet count was 317,000/μL. Though the total radiotherapy dose was given, TMZ therapy was stopped on week 5 due to refractory thrombocytopenia (grade 3) and neutropenia (grade 2). Due to delayed platelet recovery over many months, the patient was unable to continue the standard-of-care and was denied trial opportunities due to platelet counts less than 100,000/μL as many clinical trials require minimum platelet counts greater than 100,000/μL for trial participants. When the patient was not able to follow his original care plan, he experienced multiple hospitalizations due to neutropenic fever, deep vein thrombosis (DVT), and pulmonary embolism (PE). Of note, the patient had an inferior vena cava (IVC) filter placed due to his history of PE.

Surveillance imaging after radiotherapy revealed evidence of tumor progression, and the patient was initiated on concurrent therapy with bevacizumab and an Optune device. The patient's further progression of his disease led to hydrocephalus, requiring a shunt. During the shunt procedure, another biopsy was taken with hopes to get the patient onto a clinical trial. These neurosurgical procedures posed extreme complexity in the setting of severe thrombocytopenia, as the patient's platelet counts were still extremely low at 71,000/μL, and he required a transfusion before undergoing surgery to boost his platelet count to 104,000/μL. Unfortunately following surgical intervention, the patient's thrombocytopenia continued. In discussion with his hematologist, the care team tried to have eltrombopag approved by his insurance, but the insurance company denied this treatment. Overall, the patient's thrombocytopenia lasted for a total of 6 months following cessation of TMZ, which required him to undergo a total of 6 platelet transfusions. His platelet count nadir during this period was 5,000/μL. The decision was made to trial CPLE with a dose of 1 tbsp of juice twice daily with meals to encourage platelet count recovery at week 29. The specific papaya leaf extract liquid obtained was purchased through Herbal Goodness[14] and recommended by naturopathic oncologist Dr. Lise Alschuler of the Andrew Weil Center for Integrative Medicine. The 16-ounce bottle contains 40 calories, 12 g of carbohydrates, and 1,000 mg of organic papaya leaf extract per the serving size of 1 tbsp (15 mL). Neither Dr. Alschuler nor the Andrew Weil Center for Integrative Medicine has commercial interests or ties to Herbal Goodness. On CPLE-use day 2, the patient's platelets were 113,000/μL, which was the first time his platelets had been above 100,000/μL since TMZ therapy was halted. The patient's platelets consistently remained above 100,000/μL since initiating CPLE which allowed him to continue bevacizumab and Optune, as well as to receive radiotherapy for new lesions. Figure 2 demonstrates the trend in the patient's platelet count from October 2020 through July 2021. Figure 1F to J reveals MRI images taken 9 months after the patient stopped his prescribed TMZ chemotherapy regimen. The patient demonstrated compliance for the duration of his recommended CPLE treatment. He continued using CPLE until 08/27/21. Additionally, he reported no side effects and did not display any adverse toxicities to CPLE use. The patient verbally consented to this manuscript's production and publication. Consent was recorded in the patient's electronic medical record. IRB approval was obtained from the University of Cincinnati Institutional Review Board (IRB 2019-1403).

Discussion

Following temozolomide-induced thrombocytopenia, CPLE was used to successfully maintain platelet counts

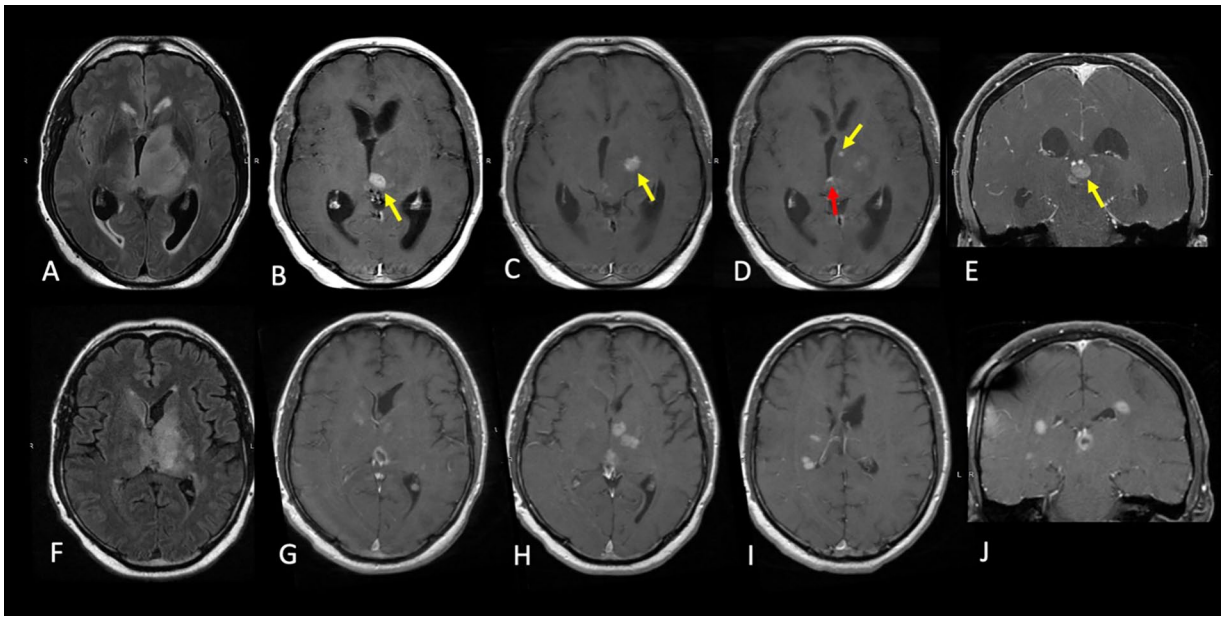

Figure 1. Axial FLAIR (A and F), axial postcontrast (B-D and G-I), and coronal postcontrast (E and J) images, before (A-E) and after chemoradiation treatment (F-J). *Before treatment*: Enhancing nodular lesions centered in the left thalamus and thalamocapsular junction (yellow arrows) with surrounding expansile infiltrative FLAIR signal alteration of the adjacent structures extending into the left superior cerebellar peduncle, basal ganglia, and medial left temporal lobe. Findings are consistent with infiltrative high-grade anaplastic astrocytoma. Punctate subependymal dissemination in the third ventricle is noted (red arrow). This results in a marked mass effect and obstructing hydrocephalus with transependymal interstitial edema. *Nine months after treatment:* Interval decrease in size of the enhancing lesions in the left thalamus and basal ganglia with decrease in infiltrative mass-like FLAIR signal hyperintensity. Multiple new enhancing lesions in the right basal ganglia and bilateral periventricular white matter are noted. Improved ventriculomegaly and resolved transependymal edema, status post shunt catheter placement.

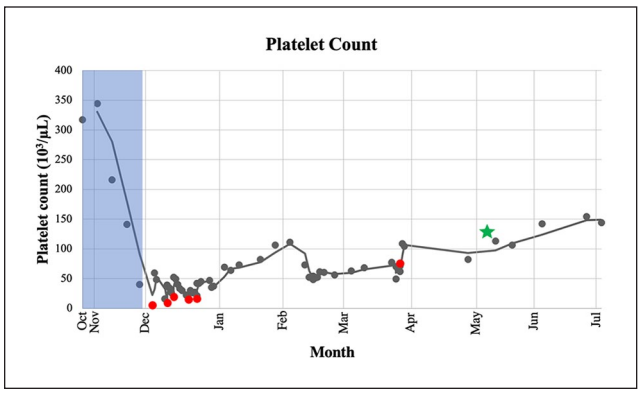

Figure 2. Platelet count graph. This graph demonstrates the trend of platelet values measured in the patient's complete blood count (CBC) labs between the dates of 10/22/20 and 07/01/21. The patient received 6 platelet transfusions; red data points indicate when a transfusion was given. The vertical blue lines indicate the date range when the patient was receiving TMZ (10/22/20-11/25/20). The green star indicates when *C. papaya* leaf extract was introduced into the patient's diet.

above 100,000/μL in a patient who was denied thrombopoietin agonist treatments by his insurance. This case report highlights a gap in patient care given that CIT patients only receive a platelet infusion at around 10,000/μL, yet platelet counts less than 100,000/μL can result in adverse outcomes.[15] Hesitancy in providing infusions arises from the potential of infusion reactions and the risk of platelet transfusion purpura with increasing numbers of transfusions. The other main treatment option for CIT is a thrombopoietin agonist, eltrombopag, but this treatment is often denied by insurance given its cost and associated hepatotoxicity. Thus, there exists a wide range of platelet counts at which infusion is not typically performed, yet adverse outcomes such as spontaneous bleeding and complications with surgery can occur. Most importantly, at this thrombocytopenic range, many clinicians will opt for a reduction in dose and frequency of the offending chemotherapeutic agent, thereby potentially impacting patient outcomes in terms of tumor progression. Alternative therapeutics such as CPLE may help to fill this treatment gap, avoiding stoppages in chemotherapy and reducing potential thrombocytopenia-associated hemorrhagic risks.

CPLE has previously been used in Southeast Asian cultures for the treatment of dengue fever-induced thrombocytopenia.[16] The mechanism of dengue-mediated thrombocytopenia is

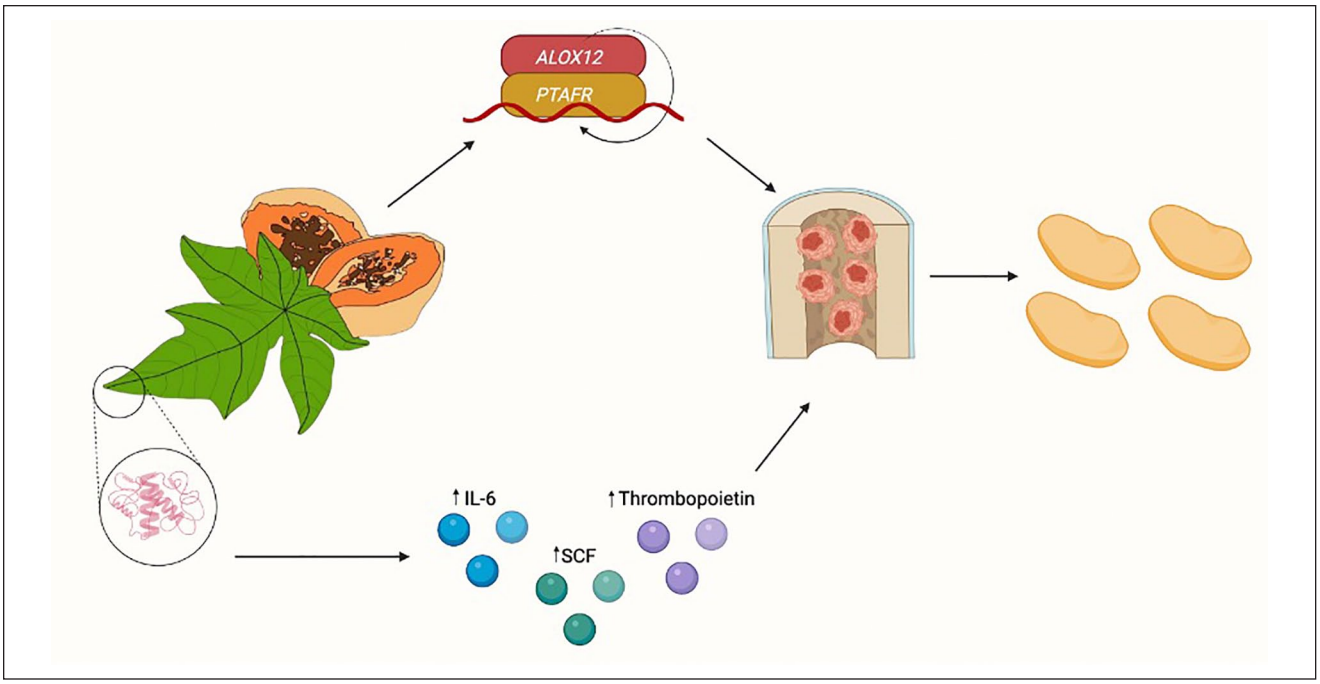

Figure 3. Proposed mechanism of action for the effects of *C. papaya*. Papain, an active constituent in CPLE may cause an increase in thrombocytic cytokines. CPLE may also upregulate *ALOX12* and *PTAFR* genes. Both potential mechanisms result in hyperactivate megakaryocytes and increased platelet counts. This image was created using BioRender.

relatively unknown, but the three outstanding hypotheses are bone marrow suppression, disruption of megakaryocyte maturation, and direct viral toxicity to platelets.[17] Given that much of the research on CPLE has been conducted in the context of dengue fever, one can attempt to glean a possible mechanism of action for CPLE in CIT from this research. One theory is that CPLE contains papain which is a protease present in unripe papaya and CPLE.[9] Papain has many uses, including tenderizing meat and supporting digestion. Its properties and the mechanism for its action have been discussed in digestive research on Caricol®, which is prepared with *C. papaya*.[18] Papain is also thought to upregulate thrombocytic cytokines such as IL-6, stem cell factor (SCF), and thrombopoietin[19-21] (Figure 3). Its survival after digestion can be inferred from a 2012 study of proteases orally administered to rats.[22] Additionally, previous research has shown that peptides and large proteins can pass through the barrier of the gastrointestinal tract; some cysteine proteases can reach the blood or lymph intact.[22] Another proposed mechanism of action for the effects of *C. papaya* on platelets involves the upregulation of the arachidonate 12-lipooxygenase (*ALOX12*) and platelet-activating factor receptor (*PTAFR*) genes[2] (Figure 3). Given that the *PTAFR* and *ALOX12* genes are expressed in megakaryocytes, this indicates that they could be precursors for platelet production in addition to their role in platelet aggregation.[8,12,23]

The novelty of the treatment makes a standard effective dose difficult to determine and thus necessitates further research. Dr. Alschuler advised on the treatment dose based on the observed effects of this dose in other patients, who did not experience any adverse toxicities. Notably, the dose recommended in this case is only ~2/3 of that discussed in the pilot studies cited above; however, only juice extract is available in the United States rather than CPLE tablets or standardized extract used in cited studies.

In the current case, we note the efficacy of CPLE as an alternative treatment for CIT in a patient ill-suited for transfusion and who was denied a thrombopoietin agonist. Further research needs to be conducted to better delineate the specific mechanism(s) of action of CPLE and the optimal treatment dose, specifically, comparing dosage comparisons between CPLE tablets and standardized extract to the juice extract available in the United States. The history of plant-based drugs is at the foundation of modern medicine with well-known examples such as Edward Stone with salicylic acid and the chemotherapy agent paclitaxel. We hope that CPLE can follow this tradition as another tool in oncologists' toolkit to treat CIT.

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Author Contributions

Manuscript preparation: A.K., R.R., Y.R., T.S., and Y.M.G. Conceptualization and supervision: L.A. and S.S.

Declaration of Conflicting Interests

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