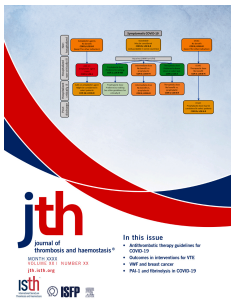
Journal Pre-proof



Management of Chemotherapy Induced thrombocytopenia: Guidance from the ISTH Subcommittee on Hemostasis & Malignancy

Gerald Soff, Avi Leader, Hanny Al-Samkari, Anna Falanga, Anthony Maraveyas, Kristen Sanfilippo, Tzu-Fei Wang, Jeffrey Zwicker

PII: S1538-7836(23)00734-1

DOI: https://doi.org/10.1016/j.jtha.2023.09.031

Reference: JTHA 439

To appear in: *Journal of Thrombosis and Haemostasis*

Received Date: 14 June 2023

Revised Date: 8 September 2023

Accepted Date: 25 September 2023

Please cite this article as: Soff G, Leader A, Al-Samkari H, Falanga A, Maraveyas A, Sanfilippo K, Wang T-F, Zwicker J, Management of Chemotherapy Induced thrombocytopenia: Guidance from the ISTH Subcommittee on Hemostasis & Malignancy, *Journal of Thrombosis and Haemostasis* (2023), doi: https://doi.org/10.1016/j.jtha.2023.09.031.

Management of Chemotherapy Induced thrombocytopenia:

Guidance from the ISTH Subcommittee on Hemostasis & Malignancy

Gerald Soff[1], Avi Leader[2], Hanny Al-Samkari[3], Anna Falanga[4], Anthony Maraveyas[5], Kristen Sanfilippo[6], Tzu-Fei Wang[7], Jeffrey Zwicker[2]

[1] Department of Medicine, University of Miami Health System/Sylvester Comprehensive Cancer Center, Miami, FL, USA
[2] Section of Hematology, Memorial Sloan Kettering Cancer Center, New York, NY
[3] Classical Hematology, Massachusetts General Hospital, Harvard Medical School, Boston, MA
[4] Department of Immunohematology and Transfusion Medicine, Hospital Papa Giovanni XXIII, Bergamo, Italy.
[5] Faculty of Health Sciences, Joint Centre for Cancer Studies, The Hull York Medical School, Castle Hill Hospital, Hull, UK.
[6] Department of Medicine, Washington University School of Medicine, Saint Louis, MO, USA
[7] Department of Medicine, University of Ottawa, Ottawa Hospital Research Institute, Ottawa, ON, Canada

Corresponding Author:

Gerald A Soff MD
Classical Hematology Service
University of Miami Health System/Sylvester Comprehensive Cancer Center
Soffer Clinical Research Building
1120 NW 14th Street, Suite 610
Miami, FL 33136

Office Telephone: 305-243-1038
Email: gas199@miami.edu

Word count: (excluding references and supplemental data): 3231

Key words (MeSH terms):

Chemotherapy, thrombocytopenia, thrombopoietin

Abstract:

Thrombocytopenia is a common adverse effect of chemotherapy. The development of chemotherapy induced thrombocytopenia (CIT) is influenced by cancer type and therapy, occurring in approximately one-third of patients with a solid tumor diagnosis and half of all patients with a hematologic malignancy. CIT may complicate the administration of chemotherapy leading to therapeutic delays or dose reductions. This guidance document, presented by the ISTH Subcommittee on Hemostasis and Malignancy, provides a comprehensive summary of the evidence and offers direction on the use of thrombopoietin receptor agonists (TPO-RAs) in various settings of CIT, including solid tumors, acute myeloid leukemia, stem cell transplant, and lymphoma. Studies have shown that TPO-RAs can improve platelet counts in CIT, but the clinical benefits of TPO-RA in terms of reducing bleeding, limiting platelet transfusion, or avoiding chemotherapy delay or dose reduction are uncertain. Further research is needed to optimize the selection of appropriate indications and study design to manage thrombocytopenia following chemotherapy.

Introduction

While cancer-directed chemotherapy is a key modality for cancer control, suppression of hematopoiesis from therapy remains a challenge and limitation. Chemotherapy-induced anemia and neutropenia may be supported with red blood cell transfusions, erythropoietin-stimulating agents, and granulocyte colony-stimulating factors [1, 2]. However, apart from platelet transfusion for selected patients with grade 4 thrombocytopenia, support for chemotherapy-induced thrombocytopenia (CIT) remains an unmet need. CIT affects approximately one-third of patients with solid tumor diagnoses and half of all patients with hematologic malignancies [3].

Many chemotherapy protocols recommend reduction of dose or delay of treatment when the platelet count is below 100×10^9/L [4]. In some studies, reduced dose intensity has been shown to adversely impact optimal progression-free survival (PFS) and overall survival (OS) in patients with cancer [4-8]. Studies of treatment or prevention of CIT have focused on the correction of thrombocytopenia and ability to administer full dose chemotherapy. Altering the dose and schedule of chemotherapy is the primary current option to reduce the risk and incidence of CIT and platelet transfusions may be used during severe nadir.

The International Society on Thrombosis and Haemostasis (ISTH) Scientific and Standardization Committee (SSC) Subcommittee on Hemostasis and Malignancy generated this guidance document on the management of CIT.

Scope and Methodology

For the purposes of generating these guidance statements, we performed a comprehensive literature review of publications related to the use of thrombopoietin receptor agonists (e.g., romiplostim, eltrombopag, avatrombopag, lusutrombopag) for treatment or prevention of CIT. Supplemental Figure 1 and Table 1 has the strategy and yield of this search.

The literature review included queries of the Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, PubMed, EMBASE, ClinicalTrials.gov, and health technology assessments from January 1995 to March 2021 [9]. The literature search of the National Library of Medicine (PubMed) was updated through March 2022, with the search strategy listed in Supplemental Table 1. 384 articles were identified through the Pubmed search, 78 articles were identified from references in those articles. Accounting for duplicates, a total of 440 articles were reviewed. We note that this guidance document does not address thrombocytopenia in low to intermediate grade myelodysplastic

syndrome where baseline thrombocytopenia is due to underlying hematopoietic stem cell defect rather than chemotherapy related.

After reviewing the available literature and summarizing the current evidence, guidance statements were generated by consensus of all co-authors, including co-chairs from the ISTH SSC Subcommittee on Hemostasis and Malignancy as well as external content experts. All guidance statements were voted for agreement and revised based on comments. After two rounds of voting, 100% agreement was achieved. Consistent with previous ISTH guidance documents, "we recommend" is used to reflect strong guidance statements supported by high-quality evidence from clinical trials, and "we suggest" reflects weaker guidance statements based on lower quality evidence or expert opinion. All guidance statements provided below were unanimous in approval by the authors.

This guidance document only addresses therapies approved by the U.S. Food and Drug Administration, or under active clinical investigation. First generation thrombopoietic agents, (recombinant human TPO (rhTPO) and a pegylated variant referred to as recombinant human megakaryocyte growth and development factor (PEG-rHuMGDF or MGDF), are not included as these are not approved and are no longer being developed outside of the People's Republic of China [9]. Nor do we address recombinant human interleukin-11 (rhIL-11) which is no longer available or being developed.

Goals of Management:

There are two primary considerations for management of CIT: 1) bleeding in the context of severe thrombocytopenia, and 2) the necessity of reduced relative dose intensity (RDI) and/or delays of cancer-directed therapy. At grade IV thrombocytopenia, (platelet count $<25 \times 10^9$/L by the Common Terminology Criteria for Adverse Events (CTCAE) [10], CIT is associated with an increased risk of bleeding. However, recent literature indicates that a platelet count of $<10 \times 10^9$/L is the level at which spontaneous bleeding rates increase and platelet transfusions should be given (reviewed in [11, 12]).

Platelet Transfusion for Chemotherapy Induced Thrombocytopenia.

Platelet transfusions are currently the mainstay of treatment of CIT. However, platelet transfusions only provide a short duration of improvement, the platelet increment is unpredictable, and platelets are a limited resource [4, 13]. Platelet transfusions convey a risk of infection and other transfusion reactions, and some patients may become refractory to platelet transfusions.[4, 13]. Although there are no prospective studies, platelet transfusion support is not practical for routine maintenance of the platelet count through a course of chemotherapy. Platelet transfusion is typically reserved for necessary invasive procedures, episodes of active bleeding, and/or severe thrombocytopenia. A platelet count trigger level of

10 x 10^9/L is usually adopted for prophylactic platelet transfusion during severe chemotherapy nadirs [12].

In a 2015 Cochrane Review, three RCTs were identified, comparing platelet transfusion thresholds of a standard trigger level of 10 x 10^9/L versus 20 or 30 x 10^9/L. A platelet transfusion threshold of 10 x 10^9/L did not increase the risk of bleeding and resulted in a decreased number of transfusions compared to a higher trigger level (20 or 30 x 10^9/L), although this was based on low-quality evidence [12]. More recent studies have further supported the recommendation of reserving platelet transfusions for patients with counts of less than 10 x 10^9/L [14].

Guidance Statements on the Use of Platelet Transfusion for Severe CIT:

1. We recommend empiric platelet transfusion for platelet count <10 x10^9/L
2. We suggest platelet transfusion for serious bleeding (WHO grade 2 or higher) in patients with less severe thrombocytopenia (e.g., <50 x 10^9/L)
3. We recommend that platelet transfusion not be administered prophylactically to maintain the platelet count to allow for full dose chemotherapy.

Thrombopoietin Receptor Agonists For CIT in Solid Tumors

Thrombopoietin receptor agonists (TPO-Ras) are a class of drugs that bind to and activate the TPO receptor, but do not contain the peptide sequence of TPO itself. The TPO receptor is also referred to as c-mpl or CD110 [15]. Currently, there are four available TPO-RAs. Romiplostim is a "peptibody", a protein comprised of a two 14 amino acid peptide sequences, that binds to and activates the extracellular domain of the TPO receptor, conjugated to the Fc region of a human IgG1 antibody to prolong the half-life. Romiplostim is administered as a subcutaneous injection, typically once weekly. Eltrombopag, avatrombopag, and lusutrombopag are orally available small molecule drugs that also bind to and activate the TPO receptor (reviewed in [15, 16]).

Four TPO-RA are now approved for one or more thrombocytopenic states, including immune thrombocytopenia, aplastic anemia, and to improve platelet counts in some patients with pre-operative thrombocytopenia. Most recently, romiplostim has been approved for treatment of hematopoietic syndrome of acute radiation syndrome. None of the TPO-RA are approved by the United States Food and Drug Administration or the European Medicines Agency for treatment of CIT. [17, 18] The National Comprehensive Cancer Network endorses consideration of romiplostim as one option for patients with CIT. [1] No other published guidelines address use of TPO-RA for CIT.

To date there has been only a single phase 3 trial reported on the efficacy of TPO-RA in CIT. In a phase 3 trial in patients (N=122) with ovarian, bladder, or lung cancer receiving chemotherapy with severe thrombocytopenia, patients were randomly assigned (2:1) to oral avatrombopag 60 mg (N=82) or placebo (N=40) once daily given 5 days before and after chemotherapy [19]. Eligibility specified thrombocytopenia ($<50\times10^9$/L) during the qualifying chemotherapy cycle but did not specify significant thrombocytopenia at Day 1 of the new cycle. This study also excluded patients with a previous history of chemotherapy-induced thrombocytopenia (platelet count $<75 \times 10^9$/L). The primary endpoint was a composite of absence of platelet transfusion, chemotherapy dose reduction of 15% or more due to thrombocytopenia, or a chemotherapy delay of 4 days or more due to thrombocytopenia [19]. Although, platelet counts were higher throughout the study with avatrombopag, the study did not meet its primary efficacy endpoint. The authors note that, "This lack of treatment difference might have been due to a high rate of spontaneous platelet count recovery in the placebo group, rather than a lack of efficacy of avatrombopag to increase platelet counts," [19].

Both eltrombopag and romiplostim have been evaluated in phase 2 clinical trials for the management of CIT. In a randomized, double-blind, multicenter phase 2 study, 183 patients receiving first-line carboplatin/paclitaxel for the treatment of advanced solid tumor malignancies were randomized to eltrombopag or placebo [20]. Eltrombopag failed to achieve the primary study endpoint of change in platelet count from day 1 in cycle 2 to the platelet nadir in cycle 2. Similarly, in a phase 2 study of 75 patients with solid tumor diagnosis receiving gemcitabine monotherapy or gemcitabine plus cisplatin/carboplatin, eltrombopag did not lead to a significant improvement in platelet nadir compared with placebo, the primary endpoint [21]. There was a non-significant trend towards greater platelet counts with eltrombopag [21]. In both trials, it was noted that the placebo cohort did not exhibit the expected rate of CIT, leading to underpowering of the studies [20, 21].

The published experience with romiplostim does suggest efficacy in improving platelet counts following chemotherapy. An open label, randomized phase 2 trial of in 60 patients with solid tumor with persistent thrombocytopenia (platelet count $<100 \times 10^9$/L) for at least 4 weeks despite chemotherapy delay compared weekly romiplostim with standard of care [22]. The initial romiplostim dose was 2 mg/kg and was titrated for a target of 100-200 $\times 10^9$/L. The primary endpoint was a target platelet count of 100 $\times 10^9$/L within 3 weeks of study drug administration. In an interim analysis, 14 of the 15 romiplostim patients (93%) achieved the primary end point of corrected platelet counts ($\geq 100 \times 10^9$/L) within 3 weeks, compared with 12.5% (1 of 8) of control patients ($P < 0.001$). The remaining patients were treated with romiplostim. In an intention to treat analysis, 85% (44 of 52) of all romiplostim treated patients corrected the platelet count within 3 weeks [22]. In a follow-up extension study, 21 patients remained on

romiplostim for 1 year or longer with 14 patients (70%) experiencing no subsequent episodes of CIT, 4 subjects had a single chemotherapy dose delay due CIT, and 2 patients required a chemotherapy dose reduction [23]. One patient experienced a proximal deep vein thrombosis, and one patient experienced multiple tumor-related ischemic events. In a single arm, phase 2 study of patients with glioblastoma, romiplostim yielded encouraging results with 12 of 20 (60%) of patients with glioblastoma who previously experienced grade 3 or 4 thrombocytopenia were able to complete the remaining planned chemotherapy without recurrent CIT [24]. In a retrospective analysis of an institutional pathway, a total of 173 patients (153 solid tumor, 20 lymphoma or myeloma) were treated with romiplostim. Romiplostim was effective in solid tumor patients: 71% achieved a romiplostim response, defined as a platelet count $\geq 75x10^9$/L and at least $30x10^9$/L higher than the pretreatment baseline [6], 79% avoided chemotherapy dose reductions or treatment delays, and 89% avoided platelet transfusions [6].

The studies with romiplostim for CIT have used weekly dosing, and within the dose range currently FDA approved for ITP (1 mcg/kg to 10 mcg/kg). [6, 18, 22, 23] Further, administration of romiplostim on the same day of chemotherapy appears to be safe and effective. No reports have addressed dosing strategies, different from the standard weekly dosing. [22, 23]

A notable difference between the reported romiplostim studies and the negative eltrombopag studies in solid tumor patients is that the three romiplostim studies did not include chemotherapy naïve patients and specified significant prior CIT as eligibility criteria [6, 22, 24].

There are no reports of studies of lusutrombopag for CIT.

Guidance Statements For Thrombocytopenia Receptor Agonists for CIT in Solid Tumors

This subcommittee acknowledges the lack of high-quality data (phase 3 trials) demonstrating efficacy for TPO-RA in the management of CIT. As such, any guidance below regarding the use of TPO-RA in management of CIT should be considered suggestions (or weak recommendations).

1. If considering use of a TPO-RA, we suggest enrollment in a clinical trial as preference.
2. If unable to enroll in a clinical trial, we suggest consideration of a TPO-RA in the setting of inadequate platelet recovery at day 1 of a chemotherapy cycle to avoid chemotherapy dose reduction or a delay of 7 or more days. (Assuming adequate neutrophil and hemoglobin recovery.)

   a. Potential use of a TPO-RA should be in patients with solid tumors where full dose chemotherapy is expected to achieve or maintain a clinically-relevant response. (Note, the use of TPO-RA has not been studied in an adjuvant setting.)
   b. Goals of therapy for use of a TPO-RA should be to achieve an adequate platelet count to avoid reduced chemotherapy dose intensity in future cycles.
   c. Once initiated, a TPO-RA should be continued for the duration of chemotherapy, with titration to the lowest dose to maintain a target platelet count between 100-200 x 10^9/L (or titrate to the platelet count to allow full relative dose intensity chemotherapy) at the beginning of each chemotherapy cycle.

3. When considering off-label use of TPO-RA (not in the setting of a clinical trial), we recommend use of romiplostim over other TPO-RAs.
4. We recommend against the initiation of TPO-RA during chemotherapy nadir of index episode as there are no data to indicate shortening of the depth or duration of an acute nadir, and there are no data on safety in this setting.

Acute Myeloid Leukemia and High-Risk Myelodysplastic Syndrome

Induction and consolidation chemotherapy for acute myeloid malignancy (AML) is highly myelosuppressive, and chemotherapy induced thrombocytopenia is a common burden. In this setting, safe and effective use of a TPO-RA could potentially have value to reduce the risk of bleeding and need for platelet transfusion. However, it has been recognized for over 25 years that the TPO receptor (also referred to as c-MPL or CD-110) is expressed on approximately 60% of AML blast cells as well as some patients with high-risk myelodysplastic syndrome [25]. A previous study demonstrated that expression of the TPO receptor in AML blast cells is associated with a markedly shorter duration of remission [25]. Therefore, activation of the TPO receptor could potentially stimulate some myeloid leukemic cells, leading to a worse cancer outcome.

The efficacy of eltrombopag in patients with acute leukemia has been evaluated in a phase 1 [26] and two phase 2 settings [27-29]. In a phase 2 study of patients with advanced myelodysplastic syndrome or acute leukemia, 98 patients were randomized to eltrombopag and 47 patients to placebo [28]. The study failed to reach the primary composite endpoint of reduction of clinically relevant thrombocytopenic events (defined as grade 3 or worse hemorrhage, platelet counts of less than 10×10^9/L, or platelet transfusions) [28]. Two patients who received eltrombopag experienced fatal serious adverse events suspected to be

study drug-related: one fatal arterial thrombosis and one fatal myocardial infarction, while there were no fatal drug-related events in the placebo arm [28]. In a randomized, double-blind, phase 2 study conducted in patients with AML receiving induction chemotherapy, 148 patients were randomized to high-dose eltrombopag 200 mg (100 mg for east Asians) or placebo, once daily [27]. Eltrombopag resulted in no improvement in achieving platelet recovery of $\geq 100 \times 10^9$/L at any point. There was a trend of worsened survival with eltrombopag (median 15.4 months) compared with placebo (25.7 months) [27].

Guidance Statements for Thrombopoietin Receptor Agonists for in Acute Myeloid Leukemia or High-Risk Myelodysplasia.

1. We recommend against the use of TPO-RA for the management of CIT in acute myeloid leukemia or high-risk myelodysplasia outside of a clinical trial.

Stem Cell Transplant

There have been a number of reports of single cases or small case series of use of a TPO-RA in patients after SCT with persistent thrombocytopenia or secondary failure of platelet recovery (SFPR). Initiation of TPO-RA treatment was initiated after significantly delayed platelet recovery. Furthermore, these cases did not have a control cohort to allow for assessment of the probability of platelet recovery without intervention [30-38].

In one phase 2 study, patients with severe persistent thrombocytopenia ($\leq$20 X 10^9/L for 7 days or platelet transfusion-dependent) for $\geq$35 days after hematopoietic stem cell transplantation (HSCT) were adaptively randomized to receive placebo or eltrombopag. There was a small, non-significant increase in platelet counts to $\geq$30 X 10^9/L (36% versus 28%) [39]. There is even less evidence on early intervention with a TPO-RA to reduce the duration or severity of thrombocytopenia nadir following auto-SCT. Only one single institutional pilot study has recently been reported [40]. In this open label, single arm study, patients undergoing autologous SCT for lymphoma or myeloma received weekly romiplostim starting day +1 after auto-SCT until the platelet count was >50 x 10^9/L without transfusion [40]. Initial romiplostim dose was 3 μg/kg, with subsequent titration until platelet recovery. The median number of days of grade 4 thrombocytopenia or days requiring transfusions was not improved, compared with historical controls.There was a significant improvement in platelet counts at days 21 and 30 but this occurred at a later stage than the intended goal of shortening the duration and depth of the platelet nadir.[40]

Guidance Statements for Thrombopoietin Receptor Agonists in Stem Cell Transplant.

1. We recommend against the use of TPO-RA for the management of CIT in HSCT outside of a clinical trial.

Lymphoma

Published experience with a TPO-RA for CIT related to lymphoma treatment is limited. One observational study compared eltrombopag with recombinant human thrombopoietin (rhTPO) and untreated controls in patients with lymphoma [41]. (The study was conducted in the People's Republic of China where rhTPO is available.) Patients who experienced grade 3 or 4 thrombocytopenia after chemotherapy were enrolled, although not randomized. By treatment day 7, both treatment cohorts exhibited greater platelet counts than control. This study suggests eltrombopag may be effective in this setting. However, the mean platelet count in the treatment and control cohorts only diverged after day 7, by which time the platelet counts in both cohorts were already improving.

Guidance Statements for Thrombopoietin Receptor Agonists in Lymphoma.

1. We recommend against the use of TPO-RA for the management of CIT during therapy for lymphoma outside of a clinical trial.

Safety of TPO-RA

Cancer patients are well known to have an increased risk of venous and arterial thrombosis. [42] In the ITP setting, use of TPO-RA may increase the risk of thrombosis. A recent systematic review and meta-analysis showed a non-significant trend towards increased rates of thrombosis in ITP patients treated with TPO-RA [43]. Therefore, it is important to focus on this potential risk. Fortunately, in the published studies of TPO-RA, no signal of increased thrombosis risk was observed [6, 19, 22, 23]. This includes the only published phase 3 trial of a TPO-RA in cancer, with avatrombopag, where no venous thromboembolism events and no increase in arterial thrombosis events were observed in the treatment arm. [19]

Tranexamic Acid

A recently reported study evaluated the potential role of the antifibrinolytic agent, tranexamic acid, in hematologic malignancies. A-TREAT (American Trial Using Tranexamic Acid in Thrombocytopenia)

was a multicenter, double-blinded placebo-controlled randomized clinical trial of tranexamic acid versus placebo (in addition to standard platelet transfusion) in patients undergoing treatment for hematologic malignancies [44]. Treatment had no significant impact on the 30day rate of World Health Organization (WHO) grade ≥2 bleeding, and no statistically significant difference in the mean number of platelet transfusions, or thrombotic events.

Guidance Statement on Tranexamic Acid for Chemotherapy Induced Thrombocytopenia:

1. We recommend against the use of prophylactic tranexamic acid for prevention of hemorrhage in CIT.

Author Role and Contributions: Gerald Soff performed initial literature review, and authored the first draft of the manuscript. Avi Leader, Hanny Al-Samkari, Anna Falanga, Anthony Maraveyas, Kristen Sanfilippo, Tzu-Fei Wang contributed to the analysis, guidance statements and manuscript writing. Jeffrey Zwicker oversaw the project, contributed to the analysis, guidance statements, and manuscript.

Conflicts of Interest/Disclosures:

G.A.S. Has received research funding to institution: Amgen, Johnson and Johnson/Janssen Scientific Affairs, Sobi/Dova Pharmaceuticals, Anthos Therapeutics. Has consulted for Johnson and Johnson/Janssen Scientific Affairs, Sobi/Dova Pharmaceuticals, Luzsana (HengruiUSA) Biotechnology, Sanofi

H.AS: Research funding to institution: Agios, Amgen, Novartis, Sobi, Vaderis.Consultancy: Agios, Forma, Novartis, Sobi, Pharmacosmos, Moderna, argenx, Rigel

A.L: Honoraria: Bayer, Leo Pharma, Pfizer, Novartis, Sanofi

A.M. has received travelling and CPD support from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, & Pfizer. Research support from Bayer, Pfizer & Bristol-Myers Squibb. Advisory boards for Pfizer, Bristol-Myers Squibb, Daiichi-Sankyo, Leo Sanofi & Bayer and fees for speaker bureau from Leo, Pfizer, BMS and Bayer.

T.F.: Advisory board honoraria from Servier and Valeo, and research funding to the institution from Leo Pharma.

J.I.Z: Research Funding: Incyte and Quercegen; Data safety monitoring boards: Sanofi, CSL Behring; Consultancy: Calyx. Advisory board participation with Pfizer/Bristol Myers Squibb (BMS) and Janssen. Is supported in part through the NIH/NCI Cancer Center Support Grant P30 CA008748

All other authors do not have stated conflicts to declare.

Source of Funding: none

References

1

Hematopoietic Growth Factors. *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)*, 2023.

2 Cairo MS. Dose reductions and delays: limitations of myelosuppressive chemotherapy. *Oncology (Williston Park)*. 2000; **14**: 21-31.

3 Kilpatrick K, Shaw JL, Jaramillo R, Toler A, Eisen M, Sangare L, Soff GA. Occurrence and Management of Thrombocytopenia in Metastatic Colorectal Cancer Patients Receiving Chemotherapy: Secondary Analysis of Data From Prospective Clinical Trials. *Clin Colorectal Cancer*. 2021; **20**: 170-6. 10.1016/j.clcc.2020.10.004.

4 Kuter DJ. Managing thrombocytopenia associated with cancer chemotherapy. *Oncology (Williston Park)*. 2015; **29**: 282-94.

5 Elting LS, Rubenstein EB, Martin CG, Kurtin D, Rodriguez S, Laiho E, Kanesan K, Cantor SB, Benjamin RS. Incidence, cost, and outcomes of bleeding and chemotherapy dose modification among solid tumor patients with chemotherapy-induced thrombocytopenia. *J Clin Oncol*. 2001; **19**: 1137-46. 10.1200/JCO.2001.19.4.1137.

6 Al-Samkari H, Parnes AD, Goodarzi K, Weitzman JI, Connors JM, Kuter DJ. A multicenter study of romiplostim for chemotherapy-induced thrombocytopenia in solid tumors and hematologic malignancies. *Haematologica*. 2021; **106**: 1148-57. 10.3324/haematol.2020.251900.

7 Denduluri N, Patt DA, Wang Y, Bhor M, Li X, Favret AM, Morrow PK, Barron RL, Asmar L, Saravanan S, Li Y, Garcia J, Lyman GH. Dose Delays, Dose Reductions, and Relative Dose Intensity in Patients With Cancer Who Received Adjuvant or Neoadjuvant Chemotherapy in Community Oncology Practices. *J Natl Compr Canc Netw*. 2015; **13**: 1383-93. 10.6004/jnccn.2015.0166.

8 Nakayama G, Tanaka C, Uehara K, Mashita N, Hayashi N, Kobayashi D, Kanda M, Yamada S, Fujii T, Sugimoto H, Koike M, Nomoto S, Fujiwara M, Ando Y, Kodera Y. The impact of dose/time modification in irinotecan- and oxaliplatin-based chemotherapies on outcomes in metastatic colorectal cancer. *Cancer Chemotherapy and Pharmacology*. 2014; **73**: 847-55. 10.1007/s00280-014-2416-x.

9 Soff GA, Ray-Coquard I, Rivera LJM, Fryzek J, Mullins M, Bylsma LC, Park JK. Systematic literature review and meta-analysis on use of Thrombopoietic agents for chemotherapy-induced thrombocytopenia. *PLoS One*. 2022; **17**: e0257673. 10.1371/journal.pone.0257673.

10 CTEP. CTEP Cancer Therapy Evaluation Program. 2022.

11 Schiffer CA, Bohlke K, Delaney M, Hume H, Magdalinski AJ, McCullough JJ, Omel JL, Rainey JM, Rebulla P, Rowley SD, Troner MB, Anderson KC. Platelet Transfusion for Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol*. 2018; **36**: 283-99. 10.1200/JCO.2017.76.1734.

12 Estcourt LJ, Stanworth SJ, Doree C, Hopewell S, Trivella M, Murphy MF. Comparison of different platelet count thresholds to guide administration of prophylactic platelet transfusion

for preventing bleeding in people with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation. *Cochrane Database Syst Rev*. 2015: CD010983. 10.1002/14651858.CD010983.pub2.

13 Goodnough LT, DiPersio JF. Issues in the management of cancer-related thrombocytopenia. *Oncology (Williston Park)*. 2002; **16**: 1558-67; discussion 70, 72-4.

14 Warner MA, Jambhekar NS, Saadeh S, Jacob EK, Kreuter JD, Mundell WC, Marquez A, Higgins AA, Madde NR, Hogan WJ, Kor DJ. Implementation of a patient blood management program in hematopoietic stem cell transplantation (Editorial, p. 2763). *Transfusion*. 2019; **59**: 2840-8. https://doi.org/10.1111/trf.15414.

15 Gilreath J, Lo M, Bubalo J. Thrombopoietin Receptor Agonists (TPO-RAs): Drug Class Considerations for Pharmacists. *Drugs*. 2021; **81**: 1285-305. 10.1007/s40265-021-01553-7.

16 Mytych DT, Park JK, Kim J, Barger TE, Boshier A, Jawa V, Kuter DJ. Assessment of romiplostim immunogenicity in adult patients in clinical trials and in a global postmarketing registry. *Br J Haematol*. 2020; **190**: 923-32. 10.1111/bjh.16658.

17 Afdhal NH, Dusheiko GM, Giannini EG, Chen PJ, Han KH, Mohsin A, Rodriguez-Torres M, Rugina S, Bakulin I, Lawitz E, Shiffman ML, Tayyab GU, Poordad F, Kamel YM, Brainsky A, Geib J, Vasey SY, Patwardhan R, Campbell FM, Theodore D. Eltrombopag increases platelet numbers in thrombocytopenic patients with HCV infection and cirrhosis, allowing for effective antiviral therapy. *Gastroenterology*. 2014; **146**: 442-52 e1. 10.1053/j.gastro.2013.10.012.

18 Al-Samkari H, Soff GA. Clinical challenges and promising therapies for chemotherapy-induced thrombocytopenia. *Expert Rev Hematol*. 2021; **14**: 437-48. 10.1080/17474086.2021.1924053.

19 Al-Samkari H, Kolb-Sielecki J, Safina SZ, Xue X, Jamieson BD. Avatrombopag for chemotherapy-induced thrombocytopenia in patients with non-haematological malignancies: an international, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Haematol*. 2022; **9**: e179-e89. 10.1016/S2352-3026(22)00001-1.

20 Kellum A, Jagiello-Gruszfeld A, Bondarenko IN, Patwardhan R, Messam C, Mostafa Kamel Y. A randomized, double-blind, placebo-controlled, dose ranging study to assess the efficacy and safety of eltrombopag in patients receiving carboplatin/paclitaxel for advanced solid tumors. *Curr Med Res Opin*. 2010; **26**: 2339-46. 10.1185/03007995.2010.510051.

21 Winer ES, Safran H, Karaszewska B, Bauer S, Khan D, Doerfel S, Burgess P, Kalambakas S, Mostafa Kamel Y, Forget F. Eltrombopag for thrombocytopenia in patients with advanced solid tumors receiving gemcitabine-based chemotherapy: a randomized, placebo-controlled phase 2 study. *Int J Hematol*. 2017; **106**: 765-76. 10.1007/s12185-017-2319-9.

22 Soff GA, Miao Y, Bendheim G, Batista J, Mones JV, Parameswaran R, Wilkins CR, Devlin SM, Abou-Alfa GK, Cercek A, Kemeny NE, Sarasohn DM, Mantha S. Romiplostim Treatment of Chemotherapy-Induced Thrombocytopenia. *J Clin Oncol*. 2019; **37**: 2892-8. 10.1200/JCO.18.01931.

23 Wilkins CR, Ortiz J, Gilbert LJ, Yin S, Mones JV, Parameswaran R, Mantha S, Soff GA. Romiplostim for chemotherapy-induced thrombocytopenia: Efficacy and safety of extended use. *Res Pract Thromb Haemost*. 2022; **6**: e12701. 10.1002/rth2.12701.

24 Le Rhun E, Devos P, Houillier C, Cartalat S, Chinot O, Di Stefano AL, Lepage C, Reyns N, Dubois F, Weller M. Romiplostim for temozolomide-induced thrombocytopenia in glioblastoma: The PLATUM trial. *Neurology*. 2019; **93**: e1799-e806. 10.1212/WNL.0000000000008440.

25 Wetzler M, Baer MR, Bernstein SH, Blumenson L, Stewart C, Barcos M, Mrozek K, Block AW, Herzig GP, Bloomfield CD. Expression of c-mpl mRNA, the receptor for thrombopoietin, in acute myeloid leukemia blasts identifies a group of patients with poor response to intensive chemotherapy. *J Clin Oncol*. 1997; **15**: 2262-8. 10.1200/JCO.1997.15.6.2262.

26 Strickland SA, Wang XV, Cerny J, Rowe JM, Rybka W, Tallman MS, Litzow M, Lazarus HM. A novel PrECOG (PrE0901) dose-escalation trial using eltrombopag: enhanced platelet recovery during consolidation therapy in acute myeloid leukemia. *Leuk Lymphoma*. 2020; **61**: 2191-9. 10.1080/10428194.2020.1762878.

27 Frey N, Jang JH, Szer J, Illes A, Kim HJ, Ram R, Chong BH, Rowe JM, Borisenkova E, Liesveld J, Winer ES, Cherfi A, Aslanis V, Ghaznawi F, Strickland S. Eltrombopag treatment during induction chemotherapy for acute myeloid leukaemia: a randomised, double-blind, phase 2 study. *Lancet Haematol*. 2019; **6**: e122-e31. 10.1016/S2352-3026(18)30231-X.

28 Mittelman M, Platzbecker U, Afanasyev B, Grosicki S, Wong RSM, Anagnostopoulos A, Brenner B, Denzlinger C, Rossi G, Nagler A, Garcia-Delgado R, Portella MSO, Zhu Z, Selleslag D. Eltrombopag for advanced myelodysplastic syndromes or acute myeloid leukaemia and severe thrombocytopenia (ASPIRE): a randomised, placebo-controlled, phase 2 trial. *Lancet Haematol*. 2018; **5**: e34-e43. 10.1016/S2352-3026(17)30228-4.

29 Platzbecker U, Wong RS, Verma A, Abboud C, Araujo S, Chiou TJ, Feigert J, Yeh SP, Gotze K, Gorin NC, Greenberg P, Kambhampati S, Kim YJ, Lee JH, Lyons R, Ruggeri M, Santini V, Cheng G, Jang JH, Chen CY, Johnson B, Bennett J, Mannino F, Kamel YM, Stone N, Dougherty S, Chan G, Giagounidis A. Safety and tolerability of eltrombopag versus placebo for treatment of thrombocytopenia in patients with advanced myelodysplastic syndromes or acute myeloid leukaemia: a multicentre, randomised, placebo-controlled, double-blind, phase 1/2 trial. *Lancet Haematol*. 2015; **2**: e417-26. 10.1016/S2352-3026(15)00149-0.

30 Bento L, Bastida JM, Garcia-Cadenas I, Garcia-Torres E, Rivera D, Bosch-Vilaseca A, De Miguel C, Martinez-Munoz ME, Fernandez-Aviles F, Roldan E, Chinea A, Yanez L, Zudaire T, Vaz CP, Espigado I, Lopez J, Valcarcel D, Duarte R, Cabrera R, Herrera C, Gonzalez-Porras JR, Gutierrez A, Solano C, Sampol A, Grupo Espanol de Trasplante H. Thrombopoietin Receptor Agonists for Severe Thrombocytopenia after Allogeneic Stem Cell Transplantation: Experience of the Spanish Group of Hematopoietic Stem Cell Transplant. *Biol Blood Marrow Transplant*. 2019; **25**: 1825-31. 10.1016/j.bbmt.2019.05.023.

31 Bortolotti M, Pettine L, Zaninoni A, Croci GA, Barcellini W, Fattizzo B. Efficacy and Immunomodulating Properties of Eltrombopag in Aplastic Anemia following Autologous Stem Cell Transplant: Case Report and Review of the Literature. *Pharmaceuticals (Basel)*. 2022; **15**. 10.3390/ph15040419.

32 Bostankolu Degirmenci B, Yegin ZA, Dikyar A, Aydin Kaynar L, Ozkurt ZN, Uyar Gocun P, Akyurek N. Eltrombopag may induce bone marrow fibrosis in allogeneic

hematopoietic stem cell transplant recipients with prolonged thrombocytopenia. *Leuk Res*. 2022; **118**: 106870. 10.1016/j.leukres.2022.106870.

33 Dyba J, Tinmouth A, Bredeson C, Matthews J, Allan DS. Eltrombopag after allogeneic haematopoietic cell transplantation in a case of poor graft function and systematic review of the literature. *Transfus Med*. 2016; **26**: 202-7. 10.1111/tme.12300.

34 Marjanska A, Czyzewski K, Debski R, Krenska A, Wysocki M, Styczynski J. The Successful Sequential Use of Plerixafor and Eltrombopag For Hematopoietic Cell Transplantation in a Child With High-risk Neuroblastoma. *J Pediatr Hematol Oncol*. 2020; **42**: e680-e2. 10.1097/MPH.0000000000001551.

35 Marotta S, Marano L, Ricci P, Cacace F, Frieri C, Simeone L, Trastulli F, Vitiello S, Cardano F, Pane F, Risitano AM. Eltrombopag for post-transplant cytopenias due to poor graft function. *Bone Marrow Transplant*. 2019; **54**: 1346-53. 10.1038/s41409-019-0442-3.

36 Master S, Dwary A, Mansour R, Mills GM, Koshy N. Use of Eltrombopag in Improving Poor Graft Function after Allogeneic Hematopoietic Stem Cell Transplantation. *Case Rep Oncol*. 2018; **11**: 191-5. 10.1159/000487229.

37 Tanaka T, Inamoto Y, Yamashita T, Fuji S, Okinaka K, Kurosawa S, Kim SW, Tanosaki R, Fukuda T. Eltrombopag for Treatment of Thrombocytopenia after Allogeneic Hematopoietic Cell Transplantation. *Biol Blood Marrow Transplant*. 2016; **22**: 919-24. 10.1016/j.bbmt.2016.01.018.

38 Yaman Y, Elli M, Sahin S, Ozdilli K, Bilgen H, Bayram N, Nepesov S, Anak S. Eltrombopag for treatment of thrombocytopenia after allogeneic hematopoietic cell transplantation in children: Single-centre experience. *Pediatr Transplant*. 2021; **25**: e13962. 10.1111/petr.13962.

39 Ahmed S, Bashir Q, Bassett R, Poon MC, Valdez B, Konoplev S, Alousi AM, Andersson BS, Ciurea S, Hosing C, Jones R, Kebriaei P, Khouri I, Kim S, Nieto Y, Olson A, Oran B, Parmar S, Qazilbash MH, Rezvani K, Shah N, Shpall EJ, Champlin R, Popat U. Eltrombopag for Post-Transplantation Thrombocytopenia: Results of Phase II Randomized, Double-Blind, Placebo-Controlled Trial. *Transplant Cell Ther*. 2021; **27**: 430 e1- e7. 10.1016/j.jtct.2021.02.004.

40 Scordo M, Gilbert LJ, Hanley DM, Flynn JR, Devlin SM, Nguyen LK, Ruiz JD, Shah GL, Sauter CS, Chung DJ, Landau HJ, Lahoud OB, Lin RJ, Dahi PB, Perales MA, Giralt SA, Soff GA. Open-label pilot study of romiplostim for thrombocytopenia after autologous hematopoietic cell transplantation. *Blood Adv*. 2023; **7**: 1536-44. 10.1182/bloodadvances.2022007838.

41 Zhu Q, Yang S, Zeng W, Li M, Guan Z, Zhou L, Wang H, Liu Y, Gao Y, Qiu S, Chen C, Li H, Zheng S, Yuan Y, Zhang H, Pan X. A Real-World Observation of Eltrombopag and Recombinant Human Thrombopoietin (rhTPO) in Lymphoma Patients With Chemotherapy Induced Thrombocytopenia. *Front Oncol*. 2021; **11**: 701539. 10.3389/fonc.2021.701539.

42 Grover SP, Hisada YM, Kasthuri RS, Reeves BN, Mackman N. Cancer Therapy-Associated Thrombosis. *Arterioscler Thromb Vasc Biol*. 2021; **41**: 1291-305. 10.1161/ATVBAHA.120.314378.

43 Tjepkema M, Amini S, Schipperus M. Risk of thrombosis with thrombopoietin receptor agonists for ITP patients: A systematic review and meta-analysis. *Crit Rev Oncol Hematol*. 2022; **171**: 103581. 10.1016/j.critrevonc.2022.103581.

44 Gernsheimer TB, Brown SP, Triulzi DJ, Key NS, El Kassar N, Herren H, Poston JN, Boyiadzis M, Reeves BN, Selukar S, Pagano MB, Emerson S, May S. Prophylactic tranexamic acid in patients with hematologic malignancy: a placebo-controlled, randomized clinical trial. *Blood*. 2022; **140**: 1254-62. 10.1182/blood.2022016308.

Table 1. Summary of Guidance Statements

Guidance Statements on the Use of Platelet Transfusion for Severe CIT:

1. We recommend empiric platelet transfusion for platelet count <10 x10^9/L
2. We suggest platelet transfusion for serious bleeding (WHO grade 2 or higher) in patients with less severe thrombocytopenia (e.g., <50 x 10^9/L)
3. We recommend that platelet transfusion not be administered prophylactically to maintain the platelet count to allow for full dose chemotherapy.

Guidance Statements For Thrombocytopenia Receptor Agonists for CIT in Solid Tumors

1. If considering use of a TPO-RA, we suggest enrollment in a clinical trial as preference.
2. If unable to enroll in a clinical trial, we suggest consideration of a TPO-RA in the setting of inadequate platelet recovery at day 1 of a chemotherapy cycle to avoid chemotherapy dose reduction or a delay of 7 or more days. (Assuming adequate neutrophil and hemoglobin recovery.)
    - **a.** Potential use of a TPO-RA should be in patients with solid tumors where full dose chemotherapy is expected to achieve or maintain a clinically-relevant response. (Note, the use of TPO-RA has not been studied in an adjuvant setting.)
    - **b.** Goals of therapy for use of a TPO-RA should be to achieve an adequate platelet count to avoid reduced chemotherapy dose intensity in future cycles.
    - **c.** Once initiated, a TPO-RA should be continued for the duration of chemotherapy, with titration to the lowest dose to maintain a target platelet count between 100-200 x 10^9/L (or titrate to the platelet count to allow full relative dose intensity chemotherapy) at the beginning of each chemotherapy cycle.
3. When considering off-label use of TPO-RA (not in the setting of a clinical trial), we recommend use of romiplostim over other TPO-RAs.
4. We recommend against the initiation of TPO-RA during chemotherapy nadir of index episode as there are no data to indicate shortening of the depth or duration of an acute nadir, and there are no data on safety in this setting.

Guidance Statements for Thrombopoietin Receptor Agonists for in Acute Myeloid Leukemia or High-Risk Myelodysplasia.

1. We recommend against the use of TPO-RA for the management of CIT in acute myeloid leukemia or high-risk myelodysplasia outside of a clinical trial.

Guidance Statements for Thrombopoietin Receptor Agonists in Stem Cell Transplant.

1. We recommend against the use of TPO-RA for the management of CIT in HSCT outside of a clinical trial.

Guidance Statements for Thrombopoietin Receptor Agonists in Lymphoma.

1. We recommend against the use of TPO-RA for the management of CIT during therapy for lymphoma outside of a clinical trial.

Guidance Statement on Tranexamic Acid for Chemotherapy Induced Thrombocytopenia:

1. We recommend against the use of prophylactic tranexamic acid for prevention of hemorrhage in CIT.