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COMMENTARY

Treatment of chemotherapy-induced thrombocytopenia with monotherapy versus combination therapy: the devil is in the details

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Recently in *Research and Practice in Thrombosis and Haemostasis*, Xia et al. [1] retrospectively analyze the outcomes of 294 patients with solid tumors receiving chemotherapy complicated by chemotherapy-induced thrombocytopenia (CIT) who were treated with either recombinant human thrombopoietin (rhTPO) or hetrombopag, a thrombopoietin receptor agonist (TPO-RA). Patients were treated at 3 centers in China and the primary outcome of the analysis was a platelet count of at least 50×10^9/L higher than the baseline count within 14 days of initiation of thrombopoietic support. The investigators found that 120 out of 146 patients (82%) treated with both rhTPO and hetrombopag achieved the primary outcome compared with 100 out of 148 patients (68%) treated with rhTPO alone. As expected, more patients in the combination group avoided chemotherapy dose reductions or treatment delays given the higher rate of platelet count recovery. There were no significant differences noted in bleeding rates or adverse events between the 2 groups. Although retrospective and observational, this is one of the largest studies on thrombopoietic support of CIT to date. The findings are novel and interesting because they suggest that the utility of combination thrombopoietic support in CIT could be more effective than monotherapy, and monotherapy has thus far been the only significantly investigated treatment paradigm in CIT [2]. However, as is the case in all CIT studies, the devil is in the details, and there are many details that must be considered. Most salient among them are patient selection and how CIT was defined, both of which must be sorted before the question of monotherapy versus combination therapy is even appropriate to ask.

Before analyzing the details of the study and contextualizing the findings with this analysis, some background is in order for readers who do not reside in China and therefore have likely never used either rhTPO or hetrombopag in a patient. rhTPO is a first-generation thrombopoietic agent, conceived shortly after the first purification of human thrombopoietin, and is given subcutaneously, generally on a daily dosing schedule (though the particulars of dosing may be indication-dependent). rhTPO and a related subcutaneously administered thrombopoietic compound, pegylated human megakaryocyte growth and development factor (PEG-rHuMGDF), were initially under development in the late 1990s for the treatment of CIT, but this development was halted in the West after a minority of patients receiving PEG-rHuMGDF developed antidrug neutralizing antibodies capable of crossreacting with endogenous thrombopoietin [3]. The few patients developing this immunologic complication developed prolonged thrombocytopenia but were successfully treated with immunosuppression, with resolution of thrombocytopenia. Importantly, this complication was not observed in patients treated with rhTPO, which ultimately completed clinical development in China, where it is now approved for CIT and immune thrombocytopenia (ITP) and where its use is recommended to treat CIT in Chinese oncologic treatment guidelines [4]. Hetrombopag is a newer thrombopoietin receptor agonist with clinical characteristics similar to eltrombopag (has food interactions, potential hepatotoxicity, chelates iron, and dose reduction is recommended in persons of East Asian descent), which is currently approved for ITP and severe aplastic anemia in China (though not yet for CIT) [5,6]. While the specific agents being used in this study are different than what are being employed and studied to treat CIT in the rest of the world (romiplostim and avatrombopag), the overarching concept (combination therapy vs monotherapy) remains relevant.

When studying CIT and when treating it in the clinic, the first step is always to identify the CIT subtype under evaluation, and there are 2 such phenotypes to consider [5]. Persistent CIT occurs when a patient presents for day 1 of a chemotherapy cycle with mild to moderate thrombocytopenia (typically 50-100 $\times$ 10^9/L) such that chemotherapy cannot be safely or confidently administered at full dose and on schedule, leading to chemotherapy dose reduction, treatment delay, or regimen discontinuation for an alternative (and usually oncologically inferior) regimen. By contrast, nadir CIT occurs when a patient is found to have severe thrombocytopenia midcycle (at least <50 $\times$ 10^9/L and often <30 $\times$ 10^9/L), which then recovers to a normal or near-normal platelet count (>100-150 $\times$ 10^9/L) by day 1 of the following cycle. Because weekly platelet count measurement is not indicated for most chemotherapy regimens, most cases of nadir CIT are clinically occult, being diagnosed only in the rare circumstance that the patient presents with bleeding or has labs performed for chemotherapy toxicity. While nadir CIT can be clinically relevant and lead to bleeding, particularly in patients who have received numerous prior cycles of multiagent cytotoxic chemotherapy, it does not usually require treatment unless the patient has a history of bleeding with deep nadirs, is receiving concomitant antithrombotic therapy that raises the threshold for concern, or has a profound nadir (<20 $\times$ 10^9/L), as recurrence of the deep nadir is quite unlikely in the subsequent cycle. This was well-demonstrated in a phase III randomized clinical trial of avatrombopag for nadir CIT, in which the placebo group and avatrombopag group both had similar proportions of patients achieve the primary endpoint (~70%) because the nadir CIT spontaneously "recovered" (did not recur) in most of the placebo-treated patients [7]. The placebo group, which had a mean nadir platelet count of 33 $\times$ 10^9/L during the cycle that qualified them to enter the study, improved to a mean nadir platelet count of 63 $\times$ 10^9/L during the interventional cycle on the study (the following cycle) despite no change in chemotherapy agents administered or their dosing. Persistent CIT on the other hand (and as its name would imply) rarely resolves spontaneously and typically recurs as severe or worse in subsequent cycles without major reductions in relative dose intensity of chemotherapy (which we know compromises oncologic outcomes). These patients are the primary population in whom thrombopoietic support is indicated, where it has been successful in previously completed studies [8–10] and where it is currently under evaluation in the ongoing RECITE (romiplostim, NCT03362177), PROCLAIM (romiplostim, NCT03937154), and ACT-GI (avatrombopag, NCT05772546) studies.

With this understanding, we can now examine the study by Xia et al. with greater nuance. This study defined CIT as any platelet count measured at <50 $\times$ 10^9/L at any time during the patient's treatment cycle, meaning that both persistent CIT and nadir CIT patients were included and without any discrimination. The fact that many of these patients were very likely at a nadir when they qualified means that many of them would probably have achieved the primary endpoint (a platelet count of at least 50 $\times$ 10^9/L higher than the baseline count within 14 days of initiation of thrombopoietic support) spontaneously without any thrombopoietic support. This study was retrospective, nonrandomized, and without a placebo/observation arm, so it is not possible to quantify how many would have recovered spontaneously, but the results of the aforementioned avatrombopag phase III study suggest that it is likely to be a substantial proportion. Given this, one can surmise that a portion of these patients did not require thrombopoietic treatment of their nadir CIT in the first place, which is important when contextualizing the 68% response rate in the rhTPO group and the 82% response rate in the rhTPO plus hetrombopag group.

Therefore, in the patients treated in this study, some did not require thrombopoietic support at all, some did not respond to either monotherapy or combination therapy, some responded to monotherapy alone, and some responded to combination therapy. It is the latter group that is of interest because the study proposes that this group contains patients in whom monotherapy alone would not have been successful and for whom there is real value in combination therapy. However, additional study is needed to define this "refractory to monotherapy but responsive to combination therapy" subgroup. The mechanisms of resistance to TPO-RAs in CIT are poorly understood and likely very different than in ITP. Patients with CIT who do not respond to TPO-RAs generally have bone marrow tumor infiltration, prior pelvic irradiation, or prior treatment with particularly myelotoxic drugs (eg, temozolomide) [8], which severely depletes the marrow progenitor pool as can be demonstrated with a dramatically elevated endogenous thrombopoietin level [11]. While there are some patients with these pathologies for whom "synergistic" thrombopoietin receptor binding could provoke a response where a single thrombopoietic agent would fail [12,13], the fraction is unknown and unlikely to be large, certainly not large enough to justify empiric combination therapy in all patients with CIT. A substantial portion of the 16% higher response rate in the combination group could be related to a more rapid response in these patients (given that the endpoint specified recovery within 14 days), while treatment with and proper dose titration of an effective monotherapy may be just as effective in the long run with a trivially longer response time. A proportion of the higher response rate in this study may also be related to limitations specific to rhTPO that are not relevant to the TPO-RAs used to treat CIT in the rest of the world (primarily romiplostim at this time) [14]. Additionally, given the experience in ITP [15–17], a strategy of switching from 1 thrombopoietic agent to another could be considered before attempting combination therapy, although again this has not been studied in CIT and seems unlikely to be successful in many treatment-refractory patients given the different reasons for treatment failure in CIT.

Lastly, practical considerations must also be considered, as these agents are expensive and carry risks including a theoretical thrombotic risk [18,19]. Therefore, combination therapy, especially given the lack of regulatory agency approvals of any available thrombopoietic agent outside of China for CIT, should be considered only in patients who fail maximal dose monotherapy. Given the current state of data for CIT and the significant limitations in the design of the study by Xia et al. [1], a monotherapy paradigm (the Figure illustrates the author's current recommended algorithm) remains the preferred treatment paradigm for the management of CIT with thrombopoietic support [20].

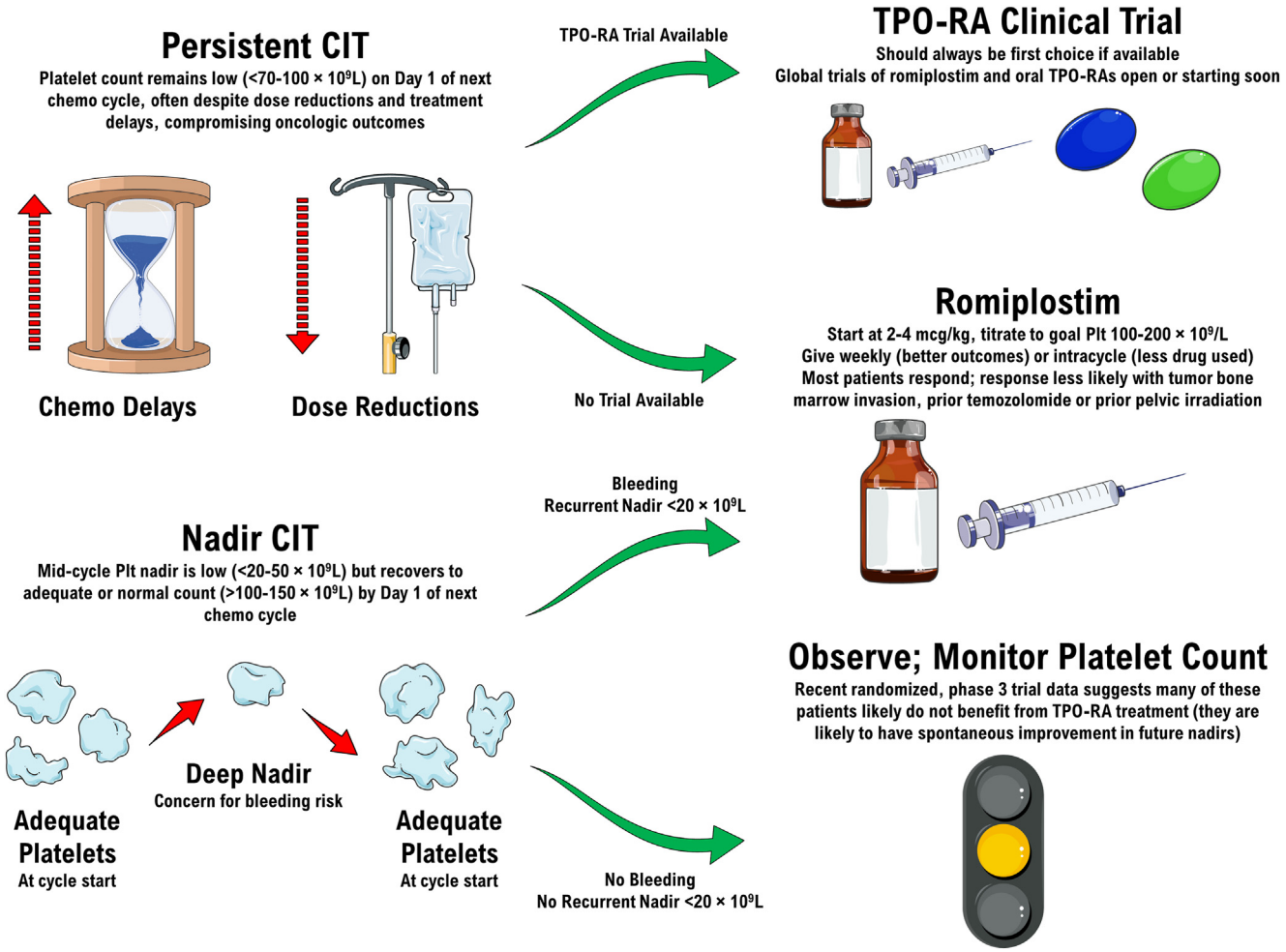

FIGURE Graphical summary of nadir CIT and persistent CIT along with the author's recommended treatment algorithm when TPO-RA therapy is considered. Adapted with permission from Al-Samkari, 2022 [20]. CIT, chemotherapy-induced thrombocytopenia; TPO-RA, thrombopoietin receptor agonist.

AUTHOR CONTRIBUTIONS

As the sole author, H.A.-S. was responsible for all aspects of the manuscript.

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