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Quarterly Medical Review

Thrombopoietic agents: There is still much to learn

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In this issue

Summary

Thrombopoietic growth factors have had an interesting development path. Many studies were done with the first generation agents and this has defined the current way that the second generation agents are used. While the first generation agents were not surprisingly targeted at chemotherapy-induced thrombocytopenia, the second generation ones have been initially developed in ITP. Surprisingly, the thrombopoietic agents have not been as simple to work with as would have been anticipated in that the relationship of treatment to the platelet count, what to expect, in what patient, and with which underlying cause of thrombocytopenia has not nearly been as straight forward as it could be. Rather than being an ''encyclopedic'' review, this manuscript is intended to provide a state of the art description of what we do and do not know in regard to important questions about usage of these still novel agents.

Already within five years of their licensure, thrombopoietic agents (TPO-A) have revolutionized the treatment of immune thrombocytopenia (ITP), the current management of hepatitis C, and seem potentially about to have major effects in other disease areas as well. The most obvious of these is treatment of aplastic anemia with TPO-A [1] but its use in non-immune inherited thrombocytopenias seems very promising as well [2]. The use of TPO-A in myelodysplastic syndrome (MDS) continues to be highly controversial and in non-myeloablative chemotherapy-induced thrombocytopenia remains to be developed as agents preserving chemotherapy dose-intensity.

Fortunately or unfortunately, these agents are not the be-all or the end-all in every condition, including ITP, but often have significant efficacy. Further studies about factors determining response and resistance to them and other issues connected with which patients respond and which patients do not, will have a major impact on their use in the future assuming that these parameters can be determined and easily identified. Both current agents are certainly expensive, as will be any novel ones in the future, and this could impact when they are used depending on whether there are other alternative treatments that are less expensive, that work as well or almost as well and that have as little in the way of toxicity.

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The TPO-A currently in use is so-called second generation and entered clinical trial in approximately 2002. In 1995, the first generation agents had been entered into clinical trial and continued in clinical trials until approximately 1999 or early 2000. There is considerable data with the first generation agents from many studies that were completed prior to their discontinuation from clinical use [3]. There is a tendency to think that issues with TPO-A are largely known based on many large randomized controlled clinical trials that have been performed *(tables I and II)*. While certainly a large amount of critical information has been obtained, a number of important questions remain unanswered in different areas. As indicated, particularly important is who would respond and who would not. A parallel question would be which toxicities will be seen and in whom will these occur. Finally, a major area that remains not well understood is whether there is a direct effect on platelet production of TPO-A. In particular, it is known that TPO-A stimulate the production of megakaryocytes and cause them to proliferate so that the number of megakaryocytes in the marrow is increased [12]. It is not known whether such megakaryocyte stimulation by TPO-A directly increases platelet production or whether platelet production increases (as does the platelet count) as a by-product of having more megakaryocytes.

TPO-A perspectives

Identifying lineage-specific growth factors has always been something of a holy grail. Technology had to improve for this to happen. Erythropoietin was initially identified in the 1980s and its clinical efficacy first demonstrated in cases of renal failure in which there was no or little erythropoietin production by diseased kidneys. At the same time, at the Walter and Eliza Hall Institute in Melbourne, scientists were working on identifying granulocyte colony stimulating factor (G-CSF) and granulocyte macrophage colony stimulating factor (GM-CSF). Soon thereafter, G-CSF was cloned at Memorial Sloan Kettering Centre and initial studies demonstrated important efficacy and proof of principle in the treatment of cases of severe congenital neutropenia. At this point, there was a delay until ingenious methods of identifying thrombopoietin were pursued and several groups cloned it simultaneously in 1994. Unlike the treatment of severe congenital neutropenia in which the G-CSF receptor was shown to be intact, it became known that the thrombopoietin receptor was defective in congenital amegakaryocytic thrombocytopenia (CAMT). In addition, there were fears that since both CAMT and TAR (thrombocytopenia and absent radii) were associated with a low but significant incidence of leukemia, these patients were not selected as initial targets for treatment. Instead, therefore chemotherapy-induced thrombocytopenia was the initial target of the first generation TPO-A. The results of the studies were able to demonstrate proof of principle but not to show clear efficacy in leukemia in the setting of myeloablative chemotherapy during and following which many platelet transfusions are given. Therefore, when these agents proved that ''thrombopoietin'' had a major role in platelet production and reversing thrombocytopenia but that it would not be easy to license in chemotherapy-induced thrombocytopenia, ITP was chosen as the primary focus when the second generation agents became available for human use. Currently, there are two agents licensed in the United States and at least 80 other countries and these agents have been licensed primarily for ITP with eltrombopag also licensed for thrombocytopenia related to hepatitis C [13]. Once TPO-A was available for trial and proven effective in ITP, a number of additional studies took place for other indications.

How did this come about and what do these agents do? First, it is of interest that thrombopoietin is considered to be the primary driver of all phases of thrombopoiesis. Other molecules contribute but it is not certain how much they contribute directly and how much they may contribute by altering the levels or the production of thrombopoietin. Other issues include in what way thrombopoietin acts on stem cells even though it stimulates generation of megakaryocyte precursors and progenitors all the way down to megakaryocytes.

Questions with some answers

In dealing with TPO agents primarily regarding treatment of ITP, this manuscript will discuss frequently asked questions. The lack of or variability in information will be considered. Opinions may be expressed but they will be couched as such and there may be areas that are sufficiently unclear that no resolution has been arrived at.

What is the actual rate of response to TPO agents in ITP?

If one looks at all of the studies done thus far that have large numbers of adults with ''typical'' persistent and chronic ITP, the response rate appears to range from 50–90% (depending upon whether one subtracts the placebo rate of response from the TPO-A rate of response or not). Probably, a realistic number for a typical patient who might be a little more difficult than average (which would be the reason why they are treated with a TPO-A) would be 60–70% or so in clinical practice. This again raises the question that it is often not clear who will respond and who will not and understanding the reason for this would be really helpful.

How long does it take to increase the platelet count?

If one gives a dose of a TPO-A to which a patient will respond well, it would nonetheless take approximately one week to observe a response [4]. However, if one is starting at a lower dose, perhaps 1–3 µg/kg/injection/week (wk) of romiplostim and increases the dose by 1 µg/kg/wk, the patient might

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