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REVIEW

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Is interleukin 3 active in anticancer drug-induced thrombocytopenia?

Abstract Interleukin-3 (IL-3) is a glycoprotein produced primarily by activated T-lymphocytes. As a hematopoietic growth factor it affects the proliferation, maturation, and survival of progenitor cells of the myeloid, erythroid, and megakaryocyte lineages. Initial studies in cancer patients with normal bone marrow using IL-3 doses of >5 μg/kg daily produced a doubling of the neutrophil count within 2–3 days and that of platelet counts by days 10–12. Phase I–II clinical trials have examined the response to IL-3 in various clinical states, and ongoing phase III studies are currently assessing the clinical relevance. In the treatment of relapsed lymphoma, small-cell lung cancer, and breast and ovarian cancer, IL-3 at doses of 5–10 μg/kg daily given mainly subcutaneously for 5–10 days has been shown to maintain chemotherapy schedules while preserving adequate granulocyte and platelet numbers in the peripheral blood. At these doses, side effects were uncommon. The translation of these observations into clinical phase III studies has been disappointing, with no clear-cut clinical advantage being observed in the treated group. This reflects the relative lack of myelosuppression seen with most current regimens for solid tumors. The role of combined treatment with IL-3 in association with granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor after cytotoxic treatment has yet to be established. However, it has been shown that they may act synergistically, resulting in significantly higher numbers of progenitor cells in the peripheral blood than when either is used alone. Combinations with IL-6 are also under study, as is the use of "cocktails" for ex vivo expansion of progenitors. This latter approach would allow single, small collections to be used for multiple infusions of progenitors and could support significant dose-intensification regimens by relieving myelosuppression. It is clear that the place of these newer cytokines in current treatment remains to be clarified.

Key words Interleukin 3 · Thrombocytopenia
Neutropenia · Dose intensification

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Introduction

The hematopoietic growth factors include the colony-stimulating factors (CSFs) and the interleukins (ILs). As chemical messengers of the immune system, growth factors function as an intercellular signaling system critical to the regulation of the hematopoietic cascade. They exert a wide range of biological effects on the growth, differentiation, self-renewal, and survival of progenitor and early pluripotential stem cells as well as on the activation of fully differentiated myeloid and lymphoid cells.

IL-3 is a glycoprotein produced primarily by activated T-lymphocytes. It regulates the proliferation and differentiation of pluripotent stem cells and committed progenitor cells of multiple hematopoietic lineages, including megakaryocytes, granulocytes, and erythrocytes. IL-3 also stimulates the function of several mature cell types, including neutrophils, eosinophils, and monocytes [17, 25]. Clinical studies have been undertaken over the past 5 years using recombinant human (rh) IL-3 either alone or in combination with other CSFs, including granulocyte-macrophage (GM)- and granulocyte (G)-CSF. These early studies indicate that IL-3 alone or in combination can significantly affect the duration and severity of thrombocytopenia and neutropenia [21]. Clinical studies currently in progress include those evaluating its use following cancer chemotherapy, after bone marrow transplantation, in bone marrow failure, and for the mobilization of hematopoietic progenitor cells into the peripheral blood. Ongoing phase III placebo-controlled studies are currently being evaluated to determine the appropriate place of IL-3 in current cancer therapy.

Table 1 Biological characterization of IL-3

1.	Interleukin 3 is also called multicolony-stimulating factor (multi-CSF)
2.	Naturally occurring IL-3 is a glycosylated protein produced by activated T-lymphocytes
3.	IL-3 has a molecular weight ranging from 14 to 28 kDa, depending on the degree of glycosylation
4.	The chromosomal location of the IL-3 gene is the long arm of chromosome 5, clustered with those encoding GM- and G-CSF

Table 2 Major actions of IL-3

1.	Stimulates early multipotential progenitors to divide
2.	Stimulates early megakaryocytic colonies to divide
3.	Primes stimulated cells to respond to late-activating cytokines
4.	Stimulates mature megakaryocytes to produce platelets
5.	Mobilizes peripheral blood stem cells
6.	Induces terminal differentiation of mature macrophages, eosinophils, and basophils
7.	Enhances mature cellular functions, including the cytotoxic, microbicidal, and tumoricidal capacities of macrophages

Structure and function of IL-3

Human IL-3 is a glycoprotein with a single polypeptide chain of molecular mass 15.4 kDa. A single disulfide bridge maintains the molecule in an active configuration. Fragments of the polypeptide are inactive and the polypeptide chain is too long to be synthesized accurately. Therefore, recombinant IL-3 is necessary for clinical use. rhIL-3 was first isolated and cloned in 1986 and has been expressed in various systems, including bacteria, yeast, and mammalian (e.g., Chinese hamster ovary) cell lines [44]. The product currently used for most studies is produced in a strain of *Escherichia coli* bearing a genetically engineered plasmid which contains the human IL-3 gene (Sandoz Pharma, Basel, Switzerland). This is a nonglycoslated form of the molecule, in contrast to those being developed in yeast and mammalian cell lines (Table 1).

IL-3 is synthesized in vivo by fewer cell types than other CSFs; this ability is predominantly restricted to T-lymphocytes, marrow stroma cells, and mast cells. Although marrow cells always express membrane receptors for IL-3, IL-3 is not detectable in serum, urine, or tissue extracts from normal individuals. Therefore, it is not possible to be certain of the role of IL-3 in healthy individuals.

The biological actions of IL-3 are similar to those of other hematopoietic growth factors and include four major actions on receptive cells: (1) growth promotion, (2) induction of differentiation and commitment, (3) enhancement of survival, and (4) modulation of the functional activity of end-stage cells [25].

IL-3 is a powerful activator of the proliferation of all myelopoietic progenitors. The effect is dose-dependent and the various progenitors have different degrees of sensitivity. Acting primarily at an early stage in hematopoietic development, IL-3 binds to specific receptors to stimulate directly the proliferation and differentiation of stem cells, including early multipotential progenitors such as colony-forming units-blast (CFU-blast). These receptors have an extracellular domain of two distinct subunits termed α and β. The β units are known to be shared by different α subunit/growth factor pairs; GM-CSF, IL-3, and IL-5 share a common β subunit, as do other growth factors. This sharing of subunits explains the shared biological functions of the different factors and the observed cytokine redundancy [35]. The progenitors most sensitive to stimulation are megakaryocytes (CFU-Meg), followed by erythroid [burst-forming units-erythroid (BFU-E)], and, finally, by granulocytic progenitors [CFU-granulocyte-macrophage (-GM), CFU-eosinophil, and CFU-basophil]. In the latter cell types, proliferative activity is stimulated only by elevated doses of IL-3. The proliferative stimulus on early progenitors is transmitted only slowly to the other compartments, suggesting that even in vivo, other molecules may play a key role in the regulation of terminal phases of these differentiation processes. IL-3 acts by modifying the sensitivity of marrow cells to the action of cytokines effective in the terminal phases of myelopoietic differentiation. These observations have been confirmed by the preliminary findings of several groups [14, 26, 41].

Preclinical studies with IL-3

The in vivo activity of IL-3 was first studied in mice, studies that confirmed the predictions of the in vitro studies [30]. Intraperitoneal injections were followed by a multilineage response in the peripheral blood, with a 10-fold increase in eosinophil counts and a 3-fold increase in neutrophil and monocyte counts being observed. Overall bone marrow cellularity and differential were not significantly changed. However, the spleen exhibited a marked increase in numbers of mature and immature hematopoietic cells. Bone marrow erythropoiesis and lymphopoiesis were reduced, but megakaryocyte and osteoclast counts were increased. These stimulatory effects on megakaryopoiesis were confirmed by other studies that looked at IL-3 alone and in combination with IL-6 [5]. Studies in primates have confirmed the findings obtained using IL-3 in mice, although the overall increase in myeloid cell counts was markedly less than that achieved with G- and GM-CSF [11, 27]. Platelet count increases were seen at higher doses of IL-3. Further studies in primates looking at sequential use of IL-3 and GM-CSF confirmed a highly synergistic effect on circulating CFU-GM, colony-forming unit-granulocyte, erythrocyte, macrophage, monocyte (CFU-GEMM), and BFU-E [15].

Studies in animals receiving chemotherapy have produced contradictory results. Some have shown improved recovery of the absolute neutrophil and platelet counts as compared with controls following combination therapy and single-agent IL-3 treatment [19]. Other studies have suggested that for full effect, combinations of other cytokines (IL-6 and GM-CSF) in conjunction with IL-3 are required for adequate neutrophil and platelet count recovery (Table 2) [45].

Dose, route, and duration of IL-3 treatment

Numerous studies have been carried out in patients with cancer and normal bone marrow cellularity to determine the appropriate dose, tolerability, and route of administration of IL-3. In some of these patients, cytotoxic therapy was given and in others it was not [1, 10]. Doses ranging from 0.25 to 10 μg/kg were given by continuous (24-h) intravenous infusion over 7 days and clearly showed a dose-dependent effect on platelets and granulocytes. Doses of ≥5 μg/kg produced significant biological effects, with a granulocyte effect being observed first by 2–3 days and a platelet effect being seen after 10–12 days from the onset of IL-3 treatment. The delayed effect on platelet counts was observed even when IL-3 was discontinued after 7 days. The maximum tolerated dose was not reached because, at the doses at which biological activity was seen, mild to moderate side effects consisting of fever, headache, and skin rash were observed. With subcutaneous use, the maximum tolerated dose was 10 μg/kg; at higher doses, severe headache, "flu-like" symptoms, and fever occurred.

Most studies carried out to monitor the response after cytotoxic chemotherapy have usually started 1 day after the last dose of treatment and IL-3 administration has been continued for 7–10 days either by intravenous infusion or by once- or twice-daily subcutaneous administration. One study looking at shorter intravenous infusions showed unacceptable toxicity at doses of >2.5 μg/kg [33], suggesting that the IL-3 concentration peaks reached with brief infusions are greater and less well tolerated than those achieved with continuous administration. In general, the studies suggest that bolus or short-term intravenous infusions are not as well tolerated as subcutaneous administration and that the latter is the recommended route for use, although continuous intravenous infusion can be used if subcutaneous injection is impractical. The results of studies comparing continuous intravenous infusion with daily subcutaneous injection indicate that the latter route is better tolerated, although the maximum tolerated dose is similar for both routes at 10 μg/kg daily [2].

Studies of duration of adminstration have shown that administration over periods of 1–4 days yields less biologic activity than is observed with treatment schedules of longer duration but that use for >10 days yields no further significant hematopoietic recovery following cytotoxic treatment [18]. These studies have led to the recommendation that IL-3 should be given as a subcutaneous injection in doses of 5–10 μg/kg daily for 5–10 days after cytotoxic cancer chemotherapy.

Potential clinical applications of IL-3

Dose-related neutropenia is frequently a dose-limiting effect of chemotherapy and is associated with significant risk of infection. Although cytokines such as G- and GM-CSF can reduce the period of neutropenia, they have little impact on the concomitant thrombocytopenia [32, 46]. Only one study, a phase I/II study of GM-CSF, has shown enhanced platelet recovery at high doses in children who are capable of tolerating such doses [13]. Therefore, IL-3 has a potential role in a number of clinical situations in patients experiencing primary or secondary hematopoietic failure. Phase III studies are currently examining patients with primary bone marrow failure, e.g., aplastic anemia, myelodysplasia, and Diamond Blackfan anemia, and secondary bone marrow failure to determine whether neutropenia and thrombocytopenia can be treated or prevented in individuals undergoing chemotherapy with or without stem-cell rescue (Table 3).

Table 3 Potential clinical indications for IL-3

1. Treatment after cancer chemotherapy to enhance dose intensification
2. In cellular support therapies after autologous bone marrow transplantation to enhance PBPC collection for ex vivo expansion of $CD34^+$ cells
3. In combination with other cytokines with GM-CSF, G-CSF, IL-6, and erythropoietin
4. In bone marrow failure, myelodysplastic syndromes, aplastic anemia, Diamond-Blackfan anemia, failure of engraftment after bone marrow transplantation

Recombinant IL-3 may also have a role in the mobilization of peripheral blood stem cells and in facilitating their harvest for use as an alternative or adjunct to autologous bone marrow transplantation (Table 3). The use of growth factors in combination has also been alluded to because, although neutrophil recovery can be reproducibly accelerated by G-CSF and GM-CSF and erythropoietic recovery by recombinant human erythropoietin, the effects on thrombocytopenia are unpredictable. However, as has been discussed, the use of IL-3 in combination with other growth factors has the potential to augment megakaryopoiesis and erythropoiesis and may also shorten the period required for hematopoietic recovery following myelotoxic treatment (Table 3). IL-3 increases the number of progenitor cells capable of responding to other growth factors, and this synergy can be adopted for potential combination treatment [1, 24].

In ongoing treatment trials, intensive chemotherapeutic regimens are being used to treat patients with chemosensitive tumors such as ovarian cancer, lymphoma, small-cell lung carcinoma, germ-cell carcinoma, and breast cancer. The purpose of such trials is to evaluate the potential for dose intensification by allowing better adherence to the intended chemotherapy schedules (Table 3). The ultimate objective is to improve patients′ response rates and disease-free survival rates as well as their quality of life.

IL-3 treatment after cancer chemotherapy

Increasing the dose of cytotoxic treatment may improve the response seen in a variety of tumors. This effect has been observed in ovarian cancer with cisplatin and carboplatin

[22], in acute myeloblastic leukemia [28], and in small-cell lung cancer particularly [31]. In these studies the probability of response and survival was directly related to the dose intensity of the drugs given. Unfortunately, with dose escalation, problems with toxicity arise; in general the predominant toxicity is myelosuppression, mainly thrombocytopenia. An early phase I/II trial conducted in Germany demonstrated that recombinant IL-3 increased platelet and neutrophil counts in patients with persistent secondary hematopoietic failure as a result of prolonged chemotherapy-induced hypoplasia [16, 20]. In a mixture of tumors (myeloma, lymphoma, germ-cell tumor, and testicular teratoma) there was a mean 6-fold increase in circulating platelets, and two of three patients dependent on platelet transfusions became platelet-independent. Side effects were mild and these initial results were encouraging.

Further studies have confirmed these results. Similar results were obtained in a subsequent study using rhIL-3 given by continuous infusion. In 20 patients with various solid tumors, doses of >4 μg/kg per day were associated with a dose-related increase in total leukocyte, neutrophil, and platelet counts, and full doses of chemotherapy were given more often than in control patients [6]. More recent studies have been carried out in patients with specific tumor types, with small-cell lung cancer, ovarian cancer, and malignant lymphoma being most widely studied.

In two major studies of ovarian cancer, dose-related increases in neutrophils and platelets were seen, and chemotherapy delay due to myelotoxicity was observed in more cycles without r-IL-3 than with IL-3 (22/45 versus 2/49; $P<0.001$) [9]. However, some studies showed an increase in toxicity when carboplatin was used; with sequential chemotherapy, IL-3 failed to prevent cumulative platelet toxicity [8]. Similar results were seen in patients with relapsed small-cell lung cancer [10, 36], with accelerated peripheral blood recovery following IL-3 administration and few side effects being encountered at IL-3 doses of ≤ 10 μg/kg. Although improvement in blood recovery was seen with good drug delivery, early results have shown no effect on the tumor response or patient survival rates.

Phase I and II studies in relapsed malignant lymphoma have also been undertaken. Studies in the Netherlands and in Germany [16, 37] have produced results similar to those reported from the other studies: hematological responses were seen; IL-3 was tolerated with only mild side effects; and postponement of chemotherapy due to insufficient hematological recovery was substantially reduced.

In these early studies the consensus was that the use of daily subcutaneous IL-3 given at doses of between 5 and 10 μg/kg once daily would hasten peripheral blood recovery. However, in many studies, patients with nonhematological malignancies are usually exposed to lower overall doses of chemotherapy than are generally used in patients with hematological malignancies. In addition, whereas blood-product support is common in the latter patients, thrombocytopenia is much less common in patients with solid tumors, occurring in only 20% of patients and often being transient. However, the original observations from the phase I/II studies, similar observations from other studies in patients with solid tumors, including non-small-cell lung cancer [42] and advanced sarcomas showing enhanced recovery [7], and the observation that this is translated into a reduced need for platelet transfusions during high-dose chemotherapy for breast cancer [18] have encouraged the development of phase III randomized studies. These will clarify the place of growth factors in cytotoxic chemotherapy and their effect on the response and survival of patients following dose intensification.

IL-3 in combination with other cytokines

IL-3 has been shown to work on earlier progenitor cells [1] and to prime a more extensive response to other cytokines such as G- and GM-CSF. IL-3 in conjunction with GM-CSF and IL-6 [12] has been shown in vivo to enhance peripheral blood recovery, a result to be expected from the understanding that we currently have of hematopoiesis and the interplay of the various growth factors. The work of Metcalf [29] has shown that in the formation of blood cells, several regulators interact in a network in which specificity, redundancy, and pleiotropism depend on the regulator, its receptor, and, most importantly, the specific situation where it has to act. The combination of IL-3 with either G- or GM-CSF has been shown in small studies to be effective in stimulating peripheral stem-cell numbers and may be an important adjunct to peripheral stem-cell harvesting [3]; larger studies are under way. However, the combination of cytokines increases their toxicity, and they need to be given sequentially rather than concomitantly. It is also likely that the use of combinations in patients with profound thrombocytopenia due to bone marrow failure may be the way forward [34].

IL-3 in cellular support therapies

With the increasing intensity of chemotherapy, thrombocytopenia has become an increasingly profound problem requiring enhanced platelet transfusion support. The use of growth factors either alone or in combination, although showing some effect, appears incapable of ameliorating cumulative marrow toxicity. This realization led to the increasing use of infused mobilized peripheral blood stem cells or marrow cells after chemotherapy. Cells have been mobilized using G- or GM-CSF alone; more recent studies have examined these in conjunction with IL-3, although IL-3 alone mobilizes cells only poorly. Growth factors have been used alone or following chemotherapy when there is enhanced "spillage" of $CD34^+$ or CFU-GM cells in the peripheral blood. Several studies now using stem cells mobilized using growth factors as an alternative source of hematopoietic support have shown a more rapid recovery of circulating neutrophils along with consistently faster platelet recovery as compared with bone marrow transplantation alone or postchemotherapy [39].

Recent studies in nonmyeloid malignancies have shown that if sufficient $CD34^+$ cells are transplanted there is a

highly predictable increase in platelet recovery, achieving a platelet count of $>20\times10^9$/l in a median period of 10 days [40]. A more recent phase III randomized study confirmed this result and also demonstrated that hospitalization time, antibiotic use, and bone marrow transplantation costs were reduced [38].

There have been two recent innovations in line with these findings. One has been the use of growth factor-mobilized peripheral blood progenitor cells (PBPCs) as a source of autologous support in patients receiving multiple cycles of high-dose chemotherapy. Treatment with PBPCs collected during an initial cycle of chemotherapy, following growth factor administration, permitted the administration of four repetitive cycles of high-dose chemotherapy, offering the possibility of a reduction in the number of treatment cycles with overall dose intensification. This type of approach has the potential to allow a wider range of patients to benefit from more rapid platelet recovery with reduced morbidity and mortality and with potential benefits in terms of tumor response [43]. The use of IL-3 in conjunction with G- or GM-CSF appears particularly effective in stimulating PBPC development.

The second approach is ex vivo generation of progenitor cells to restore hematopoiesis in patients undergoing high-dose therapy. A small number of peripheral blood $CD34^+$ cells, when grown ex vivo in a mixture of growth factors including IL-3, can supply a population of precursors that have the ability to restore blood formation in patients treated with high-dose chemotherapy. This method, which requires only a small volume of the patient's blood, may reduce the risk of tumor cell contamination, circumvent the need for leukapheresis, and allow repeated cycles of high-dose chemotherapy [4].

Conclusions

IL-3 was the first cytokine available in clinical practice that had a demonstrable effect on the incidence and severity of thrombocytopenia caused by chemotherapy and also increased the production of hematopoietic progenitor cells. Whether the phase I and phase II results will be translated into positive benefit in phase III trials remains to be seen. However, currently the intensity of treatment in the majority of solid-tumor studies is such that profound thrombocytopenia is unusual and at present only transient. This suggests that until more intensive treatments have been developed and their worth has been proven, the use of cytokines for platelet support will be less of an imperative. Initial studies have shown that IL-3 alone or in combination with G- or GM-CSF can produce better adherence to the planned doses and schedules in standard treatment and a better tolerability of higher doses. There are numerous other cytokines now being developed that may affect thrombopoiesis [34], and a more specific megakaryocyte maturation and development factor equivalent to G-CSF and erythropoietin has recently been identified [23]. Its clinical effects await evaluation, but combinations of IL-3 with other cytokines currently appear an attractive way forward in the development of strategies for enhanced treatment schedules with reduced treatment-related morbidity and mortality.

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