



HYPOTHESES

Proposed Immunology of the Spontaneous Remission of Acute Myeloid Leukemia Treated with G-CSF

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Abstract

It is suggested that the spontaneous remission of acute myeloid leukemia, particularly hypoplastic acute myeloid leukemia seen after G-CSF treatment is possibly due to G-CSF augmenting an acute inflammatory response. This acute inflammatory response is one occurring during a low count of activated platelets and a low hemoglobin.

It appears that hypoplastic acute myeloid leukemia treated with G-CSF would be more likely to result in a remission if accompanied by an acute inflammatory response. The timing between subcutaneous G-CSF administration and an acute inflammatory response seems to be crucial to obtain an optimum acute inflammatory response and the optimum activation of innate immunity.

Spontaneous remission of leukemia may be preceded with a low platelet count and anemia. A low count of activated platelets may diminish the immunosuppressive effects of activated platelets on innate and adoptive immunity. Anemia or low hemoglobin may result in anaerobic tissue respiration followed by lactic acidosis. Lactic acidosis in activating the enzyme lactate dehydrogenase and thereby dysfunctional cancer cells.

[1,2] particularly, hypoplastic acute myeloid leukemia [3-6] has been reported after treatment with hematopoietic growth factors such as Growth Colony-Stimulating Factor (G-CSF). Hematopoietic growth factors particularly, G-CSF has been used to reduce duration of neutropenia and infectious complications. G-CSF. Growth factors such as G-CSF are proteins made in the body. G-CSF stimulates the bone marrow to produce stem cells and release them in the blood. These Stem cells may develop into red blood cells, white cells and platelets. G-CSF may promote production of antigen presenting cells.

Methods

Case Reports of the spontaneous remission of acute myeloid leukemia treated with G-CSF were studied and compared to one another. Literature regarding acute myeloid leukemia was studied briefly. Objective was to find a common denominator and an immunological explanation for the spontaneous remission of acute myeloid leukemia after treatment with-CSF.

Results

It is noteworthy that those patients with acute myeloid leukemia that had a spontaneous remission after treatment with G-CSF mostly had a low platelet count and a low hemoglobin prior to treatment with G-CSF. Also, it was noted that simultaneously at the time of spontaneous remission of acute myeloid leukemia their blood had normalized (pancytopenia). Furthermore, it was noted that these spontaneous remissions were mostly accompanied by an infection. [Table 1](#) list some of the case reports of spontaneous remission of acute myeloid leukemia.

Introduction

Acute myeloid leukemia is a heterogenous disorder. It is characterized by myeloid progenitors (blasts) in the bone marrow and peripheral blood. Hypoplastic acute myeloid leukemia is defined by bone marrow hypocellularity (< 20% in trephine biopsy specimen). Hypoplastic acute myeloid leukemia trend to present with profound pancytopenia. Also, hypoplastic acute myeloid leukemia bears a low tumor cell burden. In addition, hypoplastic acute myeloid leukemia primarily affects older patients.

Spontaneous remissions of acute myeloid leukemia



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Table 1: Spontaneous remission of Acute Myeloid Leukemia.

BEFORE G-CSF ADMINISTRATION			AFTER SPONTANEOUS REMISSION		
Ref. #	Platelet/L	Hemoglobin/g/dl	Infection	Platelet/L	Hemoglobin/g/dl
REF. #1	11 × 10 ⁹ /L	7.0 g/dl	*	normal	normal
REF. #2	95 × 10 ⁹ /L	8.1 g/dl	***	normal	normal
REF. #3	24 × 10 ⁹ /L	6.6 g/dl	*	53 × 10 ⁹ /L	10.3 g/dl
REF. #4	62 × 10 ⁹ /L	3.5 g/dl	**	90 × 10 ⁹ /L	10.0 g/dl (case 1)
REF. #5	28 × 10 ⁹ /L	6.5 g/dl	Pneumonia	391 × 10 ⁹ /L	10.1 g/dl (1 st episode)
REF. #6	19 × 10 ⁹ /L	5.6 g/dl	Pneumonia	Increase PLT	Increase Hb
REF. #14	141 × 10 ⁹ /L	11 g/dl	****	330 × (10)/L	10.5 g/dl
REF. #15	1.5 × 10 ⁹ /L	5.7 g/dl	Pneumonia	181 × 10 ⁹ /L	8.3 g/dl
REF. #17	54 × 10 ⁹ /L	6.0 g/dl	*****	203 × 10 ⁹ /L	9.2 g/dl

*no infection, possible indication the low platelet count and low hemoglobin (low tissue oxygenation) as the cause of spontaneous remission; **ulceronecrotic pharyngitis with fever; ***perianal abscess; ****acute respiratory failure, all clotting parameters were normal. Possible indication of low tissue oxygenation as the initial cause of a spontaneous remission of cancer; *****pneumonia, acinetobacter baumannii and enterobacter supp. Mechanical ventilation

In a case report of spontaneous remission of acute myeloid leukemia treated with G-CSF [1] the authors noted prior to the administration of G-CSF virtual absence of megakaryocytes. Platelet count prior to G-CSF administration was 11 × 9/L. This patient spontaneous remission of acute myeloid leukemia was not accompanied by an infection.

In a case report of the spontaneous remission of acute myeloid leukemia treated with G-CSF. G-CSF was administered at a dose and frequency titrated to maintain normal counts. Prior to the spontaneous remission Patient had normal platelet count and acute respiratory failure. The patient continued for 2.5 years on single growth factor.

Discussion

It seems that those patients who had a spontaneous remission of acute myeloid leukemia had a low platelet count and a low hemoglobin prior to the administration of G-CSF and a rise of platelet count and hemoglobin at the time of a spontaneous remission. This seems to indicate an acute inflammatory response. A short and temporary low platelet (inhibition of megakaryopoiesis) followed by a rise in platelet count (thrombocytosis). G-CSF may lower the platelet count and followed by a later rise in platelet count if a complication such as bone marrow suppression is not preventing the rise of platelet count. In other words, it appears that G-CSF is augmenting what happens during an acute inflammatory response induced by an infection, a temporary drop of platelet count followed by a later rise in platelet count. In other words, it appears that G-CSF is enhancing the innate immunity in recognizing and presenting the malignant antigen during an acute inflammatory response [7].

Hypoplastic acute myeloid leukemia tends to present with a lower number of activated platelets. Therefore, a lower fresh hold of activated platelets inhibiting innate immunity and adoptive immunity. Also, hypoplastic

acute myeloid leukemia have a lower tumor cell burden. Therefore, a lower fresh hold of immune suppression.

In addition, hypoplastic acute myeloid leukemia tend to present with a lower hemoglobin. Therefore, a lower tissue oxygenation and disruption in malignant cell metabolism. Cancer cells are more dependent on iron. Therefore, low hemoglobin may disrupt cancer cell metabolism.

It is suggested the noted spontaneous remission of acute myeloid leukemia after the administration of G-SCF is possibly due to the ability of the G-SCF to enhance the acute inflammatory response in the presence of low count of activated platelets and a low tissue oxygenation due to a low hemoglobin. Therefore, a low count of activated platelets with their immune regulatory function is less likely to suppress innate immunity and adoptive immunity. In addition, malignant cells become temporary dysfunctional due to low oxygenation.

The possible reason spontaneous remissions are more likely to occur in hypoplastic acute myeloid leukemia rather than acute myeloid leukemia is possibly due to the similarity that the hypoplastic leukemic cells holds to the regressive phase of an acute inflammatory response (both are of embryonic) thereby enhancing an acute inflammatory response. possibly the reason that G-CSF may induce a remission in a myeloid leukemia and not lymphatic leukemia is that myeloid leukemia cells are of the same cell line of innate immunity while lymphatic leukemia cells are close the adoptive immunity cells. It is Noteworthy G-CSF has been reported to cause a spontaneous remission of a hypoplastic acute lymphoblastic leukemia [8]. The hypoplastic tissue simulates the regressive phase of an acute inflammatory response.

It is suggested that the association of infection and the spontaneous remission of leukemia [9] is through

the medium of activation of an acute inflammatory response. It is suggested that this acute inflammatory response is not hindered by the systemic inflammation induced by the leukemia due to a low count of activated platelet by the malignant disease and may result in the activation of a suppressed immune system in leukemia patients.

Unexplained blood clots have been noted in people without any sign or symptom of cancer and who later developed cancer. Suggesting that platelets may play a pivotal role in cancer.

Since, some of the patients with acute myeloid leukemia who achieved remission with administration of G-CSF were complicated by an infection [5], then it might not be a bad idea to accompany G-CSF with an acute inflammatory response, possibly with a tuberculin skin test followed by acute inflammatory response.

It is interesting to note that some of the case reports of spontaneous remission of acute myeloid leukemia are preceded by an infection and blood transfusion [10]. Infection is indicative of an acute inflammatory response. Transfusion was might be needed due to a low platelet count or anemia. Also, blood transfusion may also result in a graft versus host reaction that could result in a further drop in platelet count. Therefore, these spontaneous remissions of acute myeloid leukemia are possibly preceded by an infection and a low platelet count and anemia.

Infections may result in a further drop of the platelet count. If more than one infection occurs simultaneously than the platelet count my drop further. If the platelet count drops enough in cancer patients than a shift may occur from innate immunity becoming activated though an acute inflammatory response rather than becoming activated through the systemic inflammation induced by the malignant growth [11]. It is interesting to note that spontaneous remission of solid tumor may occur once there are two or more infection simultaneously [12].

Systemic inflammation induced by the cancer may disrupt the normal acute inflammatory response. Therefore, it seems a low dose of a corticosteroid such a prednisone or dexamethasone prior to treatment with G-CSF may enhance the effect of G-CSF [3,13].

Spontaneous remissions of hypoplastic acute myeloid leukemia maybe preceded by a low platelet count and a low hemoglobin. Spontaneous remission of hypoplastic acute myeloid leukemia occurs simultaneously with a rise in platelet count and a rise in hemoglobin level. G-CSF promotes stems cells maturing into platelets, red cells etc. If safe an increase in G-CSF dose might be followed by a spontaneous rise of platelets if conditions such as bone marrow suppression would not be preventing the rise of platelet count. Possibly a spontaneous rise in platelet count maybe

followed with a spontaneous remission of leukemia.

Spontaneous remissions of leukemia tend to be of short duration a few months. Rarely do these spontaneous remissions of leukemia last for a year or longer. What seems to be common among these prolonged spontaneous remissions of leukemia is a low dose of a synthetic corticosteroid such as prednisone or dexamethasone prior to the spontaneous remission [3]. It is noteworthy similarly some reports of the spontaneous remission of solid tumor are also preceded with low dose of a synthetic corticosteroid.

In summary, possibly remission of hypoplastic acute myeloid leukemia (particularly elderly patients who are not suited for intensive chemotherapy) might become more likely if the administration of G-CSF is accompanied by the following:

- (a) Check platelet count, low platelet count is essential due to the immune-suppressive effect of activated platelets.
- (b) A low dose of a corticosteroid such as prednisone prior to administration of subcutaneous G-CSF.
- (c) Induction of an acute inflammatory response. The timing between the subcutaneous G-CSF and the acute inflammatory response such as to induce an optimum acute inflammatory response and the possible optimum activation of innate immunity. An acute inflammatory response might be induced, by an endotoxin or allergen. Possibly local injection of plasma rich platelet (high leukocyte) may induce a local acute inflammatory response, safety is of consideration a low dose might be used. Use of non-live vaccines (Tetanus, Diphtheria, Singles, Pneumonia, etc.) to induce an acute inflammatory response. Safety is of consideration a very low dose might be used.
- (d) Tuberculin skin test to induce delayed type hypersensitivity.
- (e) Reactive thrombocytosis may take 3 to 4 days. If a spontaneous rise of platelets does not occur after a week of G-CSF administration. If safe a gradual increase in the dose of G-CSF [14]. If a spontaneous rise of platelets does not occur after 2 to 3 weeks than platelet transfusion might be tried.

Proposed Immunology of the Spontaneous remission of hypoplastic acute myeloid leukemia treated with G-CSF: Spontaneous remission of leukemia maybe preceded by three events. Anemia or a low hemoglobin, a low platelet count and possibly an infection such as pneumonia or septicemia. Infections such as pneumonia or septicemia may further lower the platelet count or may result in low tissue oxygenation.

Cancer cells have an anaerobic metabolism which is dependent on the enzyme lactate dehydrogenase

(subtype A). The enzyme lactate dehydrogenase is an important enzyme of the metabolic pathway of cancer cells and it results in the production of lactic acid. The enzyme lactate dehydrogenase becomes inhibited at PH levels below 7.2 and it shows high substrate inhibition. Therefore, cancer cell growth is regulated by how fast it could release lactic acid. If lactic acid builds up too fast then the enzyme lactate dehydrogenase becomes inhibited and the cancer cells become dysfunctional. Low tissue oxygenation in cases such as pneumonia or anemia or low hemoglobin results in the tissue turning to anaerobic respiration and the production of lactic acid. In unusual conditions possibly the lactic acid produced by the healthy tissue (type A lactic acidosis) can add up with the lactic acid produced by the malignancy (type B lactic acidosis) resulting in the PH dropping below 7.2 and the inactivation of the enzyme lactate dehydrogenase (subtype A). There by dysfunctional cancer cells. Since, cancer cells are more dependent on iron than normal cells the lactic acid produced by the cancer cells possibly tips the balance.

A low count of activated platelets in cancer patients diminishes the inhibitory effect of platelets on innate and adoptive immunity.

An infection or an acute inflammatory response may can act as immune boost while the cancerous growth is temporary dysfunctional and a temporary low inhibitory activity of activated platelets. Furthermore, G-CSF stimulates release of stem cells that may mature into platelets [15] that are not manipulated by the cancerous growth and may direct innate immunity and adoptive immunity to remove the cancerous growth.

Similarly spontaneous remission of solid tumors may occur after malignant tissue lactic acidosis [16,17], possibly more likely if the malignant tissue is encapsulated even if spread beyond the capsule. MRI imaging can detect presence of tumor capsule.

Caution

A hypothesis has been suggested without any experimental proof for its correctness.

Medical supervision required for Experimental Treatment.

Platelet count may drop too low and cause spontaneous bleeding.

Combination of low platelet count and injection of a non-live vaccine may result in bleeding close monitoring of patient needed.

Disclaimer

Always seek the advice of your physician or other qualified health provider with any questions you may have regarding a medical condition. Never disregard professional medical advice or delay in seeking it

because you have read this study.

This is not intended to be a substitute for medical advise, diagnosis, or treatment in regards to any patient.

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