Thrombosis Research 133 S2 (2014) S63–S69

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thomres

Thrombocytopenia in cancer patients

Howard A. Liebman*

Jane Ann Nohl Division of Hematology and Center for the Study of Blood Diseases, Keck School of Medicine of the University of Southern California, Los Angeles, CA

ARTICLE INFO

Keywords:
Thrombocytopenia
Cancer
Chemotherapy
Platelet transfusions

ABSTRACT

Thrombocytopenia is a frequent complication of cancer and its treatment. The causes of thrombocytopenia in cancer patients can be diverse and multifactorial. Systemic chemotherapy is the most frequent cause of thrombocytopenia. The degree and duration thrombocytopenia depends upon whether the chemotherapeutic treatment is myeloablative, as used in stem cell transplants, or non-myeloablative, as typically used in solid non-hematologic malignancies. Additional causes of significant thrombocytopenia include tumor involvement of bone marrow and spleen; microangiopathic disorders such as disseminated intravascular coagulation, thrombotic thrombocytopenic purpura or hemolytic uremia syndrome. Lymphoproliferative malignancies can also be associated with secondary immune thrombocytopenia. Due to the broad differential diagnosis associated with cancer related thrombocytopenia, a careful diagnostic evaluation is indicated. The goal of treatment should be to maintain a safe platelet count to allow effective treatment of the underlying malignancy, prevent bleeding complications and to minimize the use of platelet product transfusion.

Thrombocytopenia is a frequent complication of cancer and its treatment. The incidence and degree of thrombocytopenia is dependent upon the type of malignancy, stage and approach to treatment. The frequency of platelet counts less than 100 x 10^9/L can vary widely ranging from nearly 100% of patients with acute leukemia to less than 5% in patients treated for head and malignancies. In some malignant disorders the development of thrombocytopenia may be multifactorial. In lymphoproliferative malignancies, thrombocytopenia can result from splenic sequestration of platelets in patients with splenomegaly, decreased production due to bone marrow replacement and/or systemic chemotherapy, and immune-mediated platelet destruction [1]. The malignancies, treatments and other cancer-related disorders that are associated with significant thrombocytopenia are listed in table 1, The focus of this review is the diagnosis and management of the frequently encountered causes of thrombocytopenia in cancer patients.

Chemotherapy-related thrombocytopenia (CRT)

Chemotherapeutic approaches to cancer treatment can be generally divided into myeloablative and non-myeloablative chemotherapy. Bone marrow ablative therapies as used in the treatment of acute leukemia, autologous and allogeneic stem cell transplant are associated with a prolonged course of thrombocytopenia requiring platelet transfusion support. The therapeutic goal of non-myeloablative chemotherapy is to maximize tumor response with minimal bone marrow suppression. In this regards, the frequency and degree of chemotherapy induced thrombocytopenia is dependent upon the chemotherapeutic regimen, individual drug doses and number of treatment cycles given. Also the timing of the platelet nadir and kinetic of platelet recover may differ significantly depending upon the specific chemotherapeutic regimen. Regimens utilizing drugs such as carboplatin or nitrosoureas can have delayed platelet nadirs while regimens incorporating alkylating agents such as cyclophosphamide or ifosfamide are associated with earlier platelet nadirs.

Non-Myeloablative Chemotherapy

The contemporary chemotherapeutic management of most non-hematologic malignancies is to give sufficient doses of the chemotherapeutic drug(s) without inducing transfusion dependent cytopenias. However, chemotherapeutic regimens that result in NCI platelet toxicity grade 3 (platelet 25 to 49.9 X 10^9/L) and grade 4 (platelets <25 X 10^9/L) often require delays in further treatment pending platelet recover which can result in a poorer therapeutic outcome. In a retrospective study of 609 solid tumor and lymphoma patients treatment delays occurred in 22% of treatment cycles due to bleeding and in 30% of cycles due to thrombocytopenia [2]. Most of the preferred chemotherapeutic regimens utilized for the treatment of the more common non-hematologic malignancies such as colon, lung, breast and prostate have a low incidence of NCI grade 3 and 4 thrombocytopenia. For example, the two most frequently used chemotherapeutic regimens for advanced colon cancer, FOLFOX (5-fluorouracil, leucovorin, oxaliplatin) and FOLFIRI (5-flurouracil, leucovorin,

* Corresponding author at: Jane Anne Nohl Division of Hematology and Center for the Study of Blood Diseases, University of Southern California-Keck School of Medicine, Norris Cancer Hospital, RM 3466, 1441 Eastlake Ave, Los Angeles, CA90033, USA. Tel.: 323-865-3950; fax: 323-865-0060.

E-mail address: liebman@usc.edu (H.A. Liebman).

Table 1
Causes of Thrombocytopenia in Cancer Patients

Direct Cancer Effect	
	Solid tumors and hematologic malignancies with bone marrow involvement
	Splenomegaly due to tumor involvement, portal or splenic vein thrombosis
Treatment Induced:	
	Systemic chemotherapy: Myeloablative and Non-myeloablative
	Radiation
Microangiopathic Disorders:	
	DIC
	TTP/HUS
	Vasculitis
Immune Disorders:	
	ITP
	LGL
	Drugs

DIC: disseminated intravascular coagulation; TTP/HUD: Thrombotic Thrombocytopenic Purpura/Hemolytic Uremic Syndrome; ITP: Immune Thrombocytopenia; LGL: Large Granular Lymphocytic Proliferation.

irinotecan), have a combined grade 3/4 thrombocytopenia reported in 1.7% and <2% of treated patients respectively [3,4]. However, the commonly used carboplatin and Paclitaxel combination for the treatment of advanced adenocarcinoma of the lung report grade 3/4 platelet adverse events in 4.9 % of patients [5].

First line treatment of ovarian cancer with cisplatin containing regimens is associated with a >70% over all response, but most patients relapse due to platinum resistance [6]. Platinum resistance can be overcome in many of these patients by the use of dose dense (AUC>2) carboplatin [7]. However, subsequent dose dense therapy is limited by high grade (NCI 3/4) thrombocytopenia [7,8]. However, a surprising observation is that the addition of weekly paclitaxel allows for the use higher doses of carboplatin to be delivered with a platelet sparing effect [9,10]. While the mechanism of this platelet sparing effect has not been fully characterized, one report has found increased CFU meg P-glycoprotein expression and increased blood levels of bone marrow stromal cell-derived thrombopoietin in the subjects receiving paclitaxel [11].

Thrombocytopenia is also seen with newer targeted therapies [12]. Multi-kinase drugs used in the treatment of non-hematopoietic malignancies can also inhibit important cellular kinases necessary for the growth and differentiation of hematopoietic progenitor cells. Sunitinib, is a multi-targeted tyrosine kinase FDA approved for the treatment of renal cell carcinoma, pancreatic neuroendocrine tumors and gastrointestinal stromal tumors [13-15]. The drug has inhibitory activity against platelet derived growth factor receptor, c-kit and FLIT-3, kinases important in hematopoietic maintenance [16]. A systematic review found high-grade (NCI 3/4) thrombocytopenia in 117 of 1547 (7.6%) patients treated with sunitunib [17]. As might be predicted targeted therapies used for the treatment of hematologic malignancies are most often associated with a significant incidence of high grade thrombocytopenia, although the mechanisms responsible for thrombocytopenia can vary [12], HDAC inhibitors cause thrombocytopenia by delaying megakaryocyte maturation, proplatelet formation and budding [18,19].

Management of chemotherapy-induced thrombocytopenia typically involves delay or dose reduction of the chemotherapeutic drugs. Unlike myeloablative therapy, chemotherapy for non-hematologic malignancies rarely requires platelet transfusion support and major thrombocytopenic bleeding is a relatively rare complication. However, strategies that reduce the frequency and degree of thrombocytopenia could potentially improve patient outcomes by allowing more dose intensive treatment with fewer treatment delays.

Beginning in the late 1990s a number of clinical trials were undertaken to assess whether thrombopoietic cytokines (Il-3, Il-6, Il-11) could reduce the frequency and severity of CRT. Only interleukin 11 (Il-11) was approved by the US Food and Drug administration for management of CRT based on a phase II randomized, placebo controlled clinical trial in which patients were transfused for platelet counts less that 20 X 10^9/L [20]. The clinical endpoint was reduction in platelet transfusions. Daily injections of 50μg/kg of Il-11 resulted in a statistically significant reduction in platelet transfusions when compared to placebo. However, toxicities for this agent were significant including atrial arrhythmias, fluid retention, dyspnea and fatigue. [20] A clinical trial in adolescent and young adults treated for a variety of non-hematologic tumors and relapsed lymphoma with ifosfamide, carboplatin and etopside (ICE) evaluated the safety and toxicity subcutaneous Il-11 in a dose escalation protocol. The maximum tolerated dose was 50μg/kg with a similar adverse event profile as previously reported, but additional toxicities of papilledema (16%) and periosteal bone formation (11%) were also observed [21]. While both of these trial demonstrated a reduction in platelet transfusions, neither were designed to show a reduction in treatment delay, improved therapeutic outcome and the toxicity profile of Il-11 limited it clinical use in the US.

With the isolation, characterization and synthesis of thrombopoietin (TPO) in 1994 [22-24], recombinant human thrombopoietin (rhTPO) and a structurally related pegylated recombinant human megakaryocyte growth and development factor (PEG-rHuMGDF) were evaluated in a number of clinical trials [25-27]. However, although several trials of PEG-rHuMGDF in patients treated with carboplatin combination therapies showed a higher platelet nadir and shorter time to platelet recovery, with repeated cycles thrombocytopenia became the dose limiting toxicity and the use of PEG-rHuMGDF did not allow for more extended treatment [27]. Because of the development of cross-reactive antibodies against endogenous TPO, clinical assessment of PEG-rHuMGDF was halted. Several small trials of recombinant TPO in patients receiving dose intense chemotherapy also demonstrated a higher platelet nadir and a faster recovery of the platelet counts in the treated patients [28-32]. However, its value in maintaining a safe platelet count, reducing the need for platelet transfusions and preventing treatment delays due to thrombocytopenia with multiple cycles of chemotherapy was not demonstrated. In contrast to the use of these thrombopoietic cytokines in patients receiving dose intense, non-myeloablative chemotherapy, neither rhTPO or PEG-rHuMGDF showed efficacy in shortening the duration of thrombocytopenia for patients receiving myeloablative treatment for acute leukemia and stem cell transplantation [33-37].

A new generation thrombopoietic agents structurally unrelated to TPO, but capable of stimulating the TPO receptor with an excellent safety profile have been developed and subsequently two drugs, romiplostim and eltrombopag, have been approved for the treatment of immune thrombocytopenia (ITP) and thrombocytopenia associated with hepatitis C-related thrombocytopenia [38-40]. Because of their excellent safety as documented in over 8 years of use in patients with ITP, several exploratory studies have been undertaken to evaluate their use in CRT. Preliminary reports of small phase I/II studies document their safety with some efficacy in CRT [41-44].

Myeloablative Chemotherapy

The primary goal of thrombocytopenic management following myeloablative chemotherapy is the prevention of major bleeding