Complications of Cancer Therapy: Best Practices in Prevention and Management

Kanika Sood Sharma
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Preface

Introduction

Cancer is one of the leading causes of mortality and morbidity worldwide. In India, majority of cancer patients present in advanced stage of disease which requires multi-modality treatment for management. There has been an increase in the medical care related to complications of this disease in last decade. The word "Complications" classically is defined as a medical problem that occurs during a disease, or after a procedure or treatment. It may be a direct outcome of the disease and its treatment or may be unrelated to it. These medical problems are unwanted, undesirable, unexpected/expected and above all unintended.

Some complications are referred to as accompaniments of treatment which fall in the category of expected side effects. The occurrence of these cannot be avoided but the intensity may be reduced by precautionary measures.

At the present era, financial toxicities which is described as the harmful effect of high cost of treatment on person's quality of life also comprise an important aspect of cancer treatment. Compared to a decade ago, patients with cancer are receiving expensive molecules and the list is growing. Inpatient hospitalizations, due to treatment complications have been the major drivers of the costs of cancer care. When compared with individuals without a cancer, cancer survivors have higher expenditure, even years after diagnosis. Early recognition and management of adverse events of cancer treatments are essential for optimal cancer care.

Types of Complications

Almost all effective medications have the potential to produce toxicity or side effects, either at therapeutic dose or at levels that exceed the therapeutic doses. All the modalities of cancer treatment (surgery, radiation, chemotherapy/immunotherapy/targetted therapy) can cause complications. By virtue of onset the complications may be acute which appear over a period of days, chronic or late which appears over a period of months or years after completion of cancer treatment. Direct complications may be an untoward effect of the malignancy where the invasion of the tumour can cause mechanical compression of the structure adjacent to it. Whereas

indirect complications include systemic manifestations of the disease or related to the treatment sequelae. Some complications are attributed to specific procedures or technique. Cancer treatment entails multi-modality treatment which exposes the patients to array of procedures which interact to compound the side effects.

One such example is chemotherapy-induced neutropenia which can be aggravated/amplified with the usage of concurrent chemotherapy along with radiation therapy. Similar interaction of different treatment modalities is seen in aggravation of pneumonitis in patients receiving taxanes and thoracic radiation.

Incidence of Complications

Treatment-related side effects in routine care are common, continue throughout routine clinical care. The incidence of complications is understated due to underreporting by the patients as well as clinicians. Most patients consider side effects as a part and parcel of the cancer treatment and do not seek consultation for the same. There is also a disparity in the incidence of complications reported by physician and the patient which is evident many studies reporting treatment-related toxicities.

Acute chemotherapy toxicity can have negative effects for the patients and the health economy. Incidence of Grade III/IV acute toxicities have been reported in 35.6% of patients. The rate of hospital admission due to toxicity and go up to 13%. Nausea and fatigue are the most common side effects, along with diarrhoea and constipation. The highest hospitalization is required due to sepsis, pneumonia and acute kidney injury. A study has reported 7.5% deaths are related to chemotherapy.

Acute effects begin within 1 or 2 weeks after starting RT and often are inflammatory or reflect the depopulation of rapidly growing epithelial cells. There is usually a direct relationship between the radiation dose and volume to normal tissue and risk of toxicity. Type and incidence of complications depend on the site of cancer and modality of treatment employed.

Late side effects in adult cancer survivors and childhood cancer survivors will vary depending on the type of cancer and type of treatment. Late effects of RT often reflect fibrosis, vascular injury or gradual changes in slowly dividing tissues. Residual DNA damage may rarely cause delayed carcinogenesis. Fatigue (15–90%) and mental health issues (80%) are common long-term side effects associated with cancer treatment. Common late side effects of breast cancer treatment include lymphoedema, cardiotoxicity, fatigue, neuropathy, cognitive dysfunction, premature menopause and infertility, bone and musculoskeletal issues. Long-term side effects for colorectal cancer survivors include bowel, bladder, sexual dysfunction, complications related to ostomy, neuropathy and mental issues. Common side effects in Head and Neck cancer survivors include musculoskeletal and neuromuscular dysfunction, upper gastrointestinal dysfunction, lymphoedema, sleep apnoea, speech defects, oral health issues and mental health issues. Common long-term effects of prostate cancer include urinary, sexual or bowel dysfunction and mental issues.

Predictive Indicators

Some indictors can predict the higher incidence of certain complications and can forewarn the clinician. There are many factors which dictate the incidence of complications, and these include the pre-existing medical condition, nutritional status, social support and socio-economic status. Severity of the side effects may vary depending on the health and nutritional status of individual. The manifestation of toxicity depends on both cellular characteristics and affected organ's anatomy and physiology. Predictive indicators can be broadly classified as-patient related, tumour related and treatment related.

Pharmacogenomics or a patient's genetic composition strongly influences how chemotherapeutic agents are absorbed, metabolized and excreted by the body.

Disease site and number of chemotherapy agents are important factors which decide the likelihood of toxicity. These factors need to be accounted during formulation of the treatment care plan.

Future Considerations

With improved screening and treatment, the number of cancer survivors are expected to increase. These side effects often have significant impact on survivor's quality of life, morbidity and overall mortality. It is essential to identify both the immediate and late side effects of treatment to plan treatment management more comprehensively. Technological advancements in external-beam RT delivery, including intensity-modulated RT (IMRT), stereotactic RT (stereotactic RT and stereotactic body RT), image-guided brachytherapy and proton therapy have decreased RT toxicity by dramatically improving the ability to deliver RT that maximizes tumour dose and minimizes organ dose. The adoption of the best practices with incorporation of the preventive measures can reduce the incidence or the severity of complications. Planned health-education for patients with cancer can help us provide effective and evidence-based care to cancer patients.

New Delhi, India — Kanika Sood Sharma
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- Vedika and Zian (children of Dr Raajit)
- Gaurika and Aayansh (children of Dr Kanika and Dr Gaurav)

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Part I

Radiation and Chemotherapy Related Complications

1 Chemotherapy-Induced & Radiotherapy-Induced Thrombocytopenia

Sarita Rani Jaiswal and Mahak Agarwal

Abbreviations

CIT	Chemotherapy induced thrombocytopenia
RIT	Radiotherapy induced thrombocytopenia
RDI	Relative Dose Intensity
TPO	Thrombopoietin
TPO-RA	Thrombopoietin-receptor agonists

1.1 Introduction

Thrombocyte is one of three major cellular components of blood produced in the bone marrow. They not only help in coagulation or regulation of haemostasis, but they mediate between the vascular system, the immune system and hemostasis [1]. Following damage to there adherence of the activated platelets to the surface of the damaged vessel and with release of various factors which causes simulation of coagulation cascade is stimulated and ultimately clot formation [2, 3]. As the clot

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grows, there is narrowing of the blood vessel which prevents blood loss. This process is called coagulation [3]. The platelet counts are in the range of 150,000 to 350,000 platelets per microliter [4]. Thrombocytopenia is a condition or a disorder in which the platelet count is decreased below the normal lower range. The formation of blood clots is impaired, hence body is unable to control bleeding. When the count gets below 10,000 platelets per microliter, bleeding can occur without trauma at any place including the brain [5]. CIT is a disorder that develops as an adverse effect of myelosuppressive chemotherapy [6]. These chemotherapeutic drugs not only kill cancer cells, they can also damage the platelet-forming cells in the bone marrow leading to damage in the process of megakaryopoiesis [7]. Thrombopoietin (TPO) is a predominant cytokine which is responsible for regulation of platelet counts [8]. The severity of CIT or RIT depends on the type of chemotherapy, intensity of the used drugs and the duration of treatment. Fortunately, CIT can be managed with platelet transfusions, additional medications, such as thrombopoietin agonists [9].

1.2 Incidence

The incidence of CIT varies widely depending on the agent or the combination of agents employed. In a study by Rong Lu et al., the incidence of most commonly used regimens which result in thrombocytopenia were 92.3%, 89.7%, 89.7% and 69.7% with DHAP (dexamethasone, cytarabine, cisplatin), ICE (Ifosfamide, carboplatin, etoposide), GDP (gemcitabine, dexamethasone, cisplatin) and Gemox (gemcitabine, and oxaliplatin) respectively [10].

1.3 Pathophysiology of Chemotherapy-Induced Thrombocytopenia

1.3.1 Reduces Platelets Production

It's important to understand the mechanism of CIT, as how platelets are made (Fig. 1.1) and not all chemotherapeutic drugs cause thrombocytopenia through the same mechanism. Stem cells differentiate into cells committed to megakaryocyte differentiation known as megakaryocyte colony-forming cells (MK-CFCs). These cells stop their mitotic divisions and enter into a process of endomitosis, leading to polyploid precursor cells with multiple times the normal diploid DNA content, which matures into large megakaryocytes. Finally, platelets are produced from the shredding of mature megakaryocytes; either a portion of the megakaryocyte membrane buds off into the sinusoid of bone marrow to produce platelets or mature megakaryocyte extrude long cytoplasmic processes through endothelial cells and large strands of platelet material (proplatelets) are released into the circulation (Fig. 1.1). These proplatelets eventually becoming mature platelets, possibly

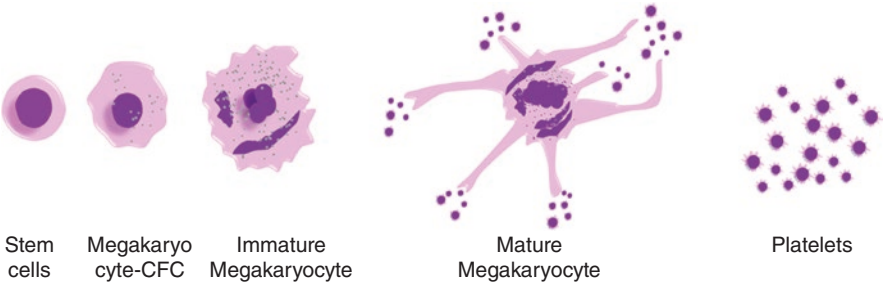

Fig. 1.1 Maturation of megakaryocyte and platelet production. Differentiation of stem cells led to megakaryocyte colony-forming cells (MK-CFCs) formation. MK-CFCs stop their mitotic divisions and enter into a process of endomitosis to form polyploid precursor immature megakaryocyte. These polyploid immature megakaryocyte precursor cells then mature into large mature megakaryocytes. Finally, platelets are produced from the shredding of mature megakaryocytes

through fragmentation in the lung. Different chemotherapy drugs have been seen to affect the megakaryocyte and platelet production pathway at different steps. Alkylating agents such as busulfan and carboplatin affect pluripotential stem cells. Cyclophosphamide spares hematopoietic stem cells because of their abundant levels of aldehyde dehydrogenase, but affects later megakaryocyte progenitors. The antibody-drug conjugate T-DM1 (trastuzumab [T] coupled to the microtubule toxin emtansine [DM1]) causes grade 3 or higher thrombocytopenia within one week in about 13% of patients by inhibiting megakaryocyte growth and differentiation. T-DM1 is internalized into megakaryocytes via the FcgRIIa receptor or by pinocytosis where it releases DM1, which inhibits megakaryocyte polyploidization and growth. Bortezomib, a proteosome inhibitor neither effect on stem cells nor megakaryocyte maturation but does inhibit NF-kB, which is a final regulator of platelet shedding. Hence a short duration of thrombocytopenia is observed.

1.3.2 Increases Platelets Destruction

Few of experimental chemotherapy agent like ABT-737 reduces the activity of the anti-apoptotic protein "Bcl-xL" and rapidly induces platelets to undergo apoptosis. After a single dose of ABT-737, platelets dropped to 30% of baseline by 2 h and re-turned to baseline after 72 h. This was not due to platelet activation. Rather, caspase-mediated apoptosis was induced with rapid appearance of phosphatidylserine on the platelet surface and clearance of these cells from the circulation by the reticuloendothelial system in the liver. The antibody-drug conjugates gemtuzumab ozogamicin (anti CD33) and inotuzumab ozogamicin (anti CD22) are both associated with acute thrombocytopenia (platelet counts dropping by 86% in 3–4 days in monkeys) and sinusoidal obliteration syndrome due to acute hepatic sequestration of platelets. Several data also show that etoposide also increases platelet apoptosis

by reducing Bcl-x (L) activity. Finally, chemotherapy may accelerate platelet clearance by immune mechanisms [11]. The administration of single-agent fludarabine in lymphoma has been noted to produce an antiplatelet antibody-mediated ITP in up to 4.5% of patients. This ITP is commonly responsive to rituximab. ITP secondary to use of chemotherapy drugs have also been documented in certain circumstances. This leads to production of a drug-dependent antiplatelet antibody, causing platelet destruction, like by the drug oxaliplatin. However this effect is uncommon and needs yet to be proven.

1.4 Radiation Induced Thrombocytopenia (RIT)

Study by Chen F et al., demonstrated that radiation induced endothelial cell injury contributes to the slow recovery of platelets after radiation; it provides a deeper understanding into the pathogenesis of thrombocytopenia induced by radiation [12]. They also demonstrated that the supplementation of exogenous VEGF significantly promoted faster migration and platelet production of MKs toward the vascular niche and a rapid recovery of the platelet level in a radiation-induced thrombocytopenia (RIT) mouse model. Another study by Lambert MP. et al., shown that platelet factor-4 (PF4) is released by the damaged megakaryocytes locally, which leads to inhibition of platelet recovery [13]. Platelet factor 4 (PF4) is a negative autocrine in vivo regulator of megakaryopoiesis. Individuals with high level of PF4 may essentially be sensitive to develop thrombocytopenia whenever there is injury to the bone marrow. Blocking PF4 enhances platelet recovery while released PF4 from megakaryocytes limits the efficacy of TPO. This is possibly due to increased release of PF4 stimulated by TPO.

1.5 Guidelines for Platelet Transfusion

Initially, the recommended guideline for cut-off value of platelet transfusion was below 20,000/μL. Later, it was seen that there is an increased risk of bleeding, when the platelet count is less than 5000/μL and this risk of bleeding does not seem to change significantly between 10,000/μL and 100,000/μL [14]. It is also evident that platelet count of 7000/μL is necessary for the interaction with the endothelium. We follow the guidelines indicating platelet count less than 10,000/μL in our institution. However, it is important to check the platelet count manually as well, due to variability in platelet size following recovery from myelosuppression, resulting in falsely low platelet counts generated by standard cell counters (Table 1.1) [14].

Table 1.1 Triggers for platelet transfusion

Platelet concentration	Patient population
$<5 \times 10^9$ cells/L	All patients who are even not bleeding and clinically stable
$<10 \times 10^9$ cells/L	Patients with fever or post-hematopoietic cell transplantation or on chemotherapy
$<20 \times 10^9$ cells/L	Patients receiving heparin; all outpatients or those who are to be discharged
$<50 \times 10^9$ cells/L	Patients who are actively bleeding or who will undergo invasive procedure within the next 4 h
$<100 \times 10^9$ cells/L	Neurosurgical patients
Any	Patients with dysfunctional platelet count (e.g., medication, disease-related, after bypass)

1.6 Evolution of Agents Directed at Thrombopoietin to Combat Thrombocytopenia

The clinically relevant TPO molecule development has occurred in 2 phases. (1) Recombinant TPO molecule (2) Recent TPO molecule. Amongst the recombinant TPO molecule, the PEG-rhMGDF is a non-glycosylated protein comprised of 153 amino acids coupled with polyethylene glycol and rhTPO is glycosylated TPO protein made in Chinese hamster ovary (Fig. 1.2). Both produced marked improvement on platelet counts and reduced the period of thrombocytopenia. The development of both was stopped in Europe and the USA due to rising titre of neutralising antibodies against PEG-rhMGDF, creating TPO deficiency and thrombocytopenia. However, rhTPO is continued in China and is licenced for CIT. Despite early failure, newer TPO molecules known as TPO-RA were developed with less side effect, like Romiplostin, eltrombopag, avatrombopag, heterombopag. TPO receptor (c-mpl) are found in all megakaryocytic cell lines, the CD34 leukemic cell lineKM1-2, and hepatocellular carcinoma cell line (Hep3B) and also on fetal liver cells and brain. The TPO receptor exists as an inactive dimer with proximal and distal HRD1 & HRD2 (hematopoetic receptor domain 1 and 2). Romiplostin and rhTPO bind to HRD2 where as other TPO-RA bind to transmembrane region of the receptor. Binding of TPO-RA to distal hematopoietic receptor domain 2 receptor domains (HRD2), or to the transmembrane region of the receptor, triggers a change in conformation of receptors and a number of signal transduction pathways, including activation of the JAK-STAT signalling pathway, which induce proliferation and differentiation of megakaryocytes. This leads to increase in platelet production (Fig. 1.3).

There are currently two approved molecules for treatment of thrombocytopenia targeting the TPO receptor. Eltrombopag was licenced in 2008 for thrombocytopenia due to chronic ITP. Romiplostim is a “peptibody” created by inserting 14 amino

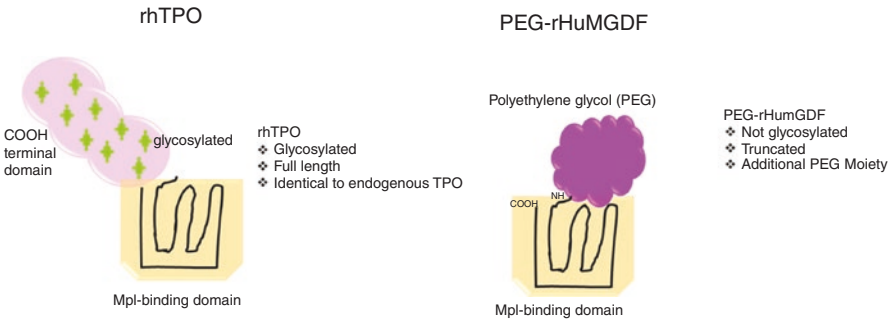

Fig. 1.2 Structure of chemotherapy drugs. Detailed composition of recombinant human thrombopoietin (rhTPO) and pegylated recombinant human megakaryocyte growth and development factor (PEG-rHuMGDF) drugs

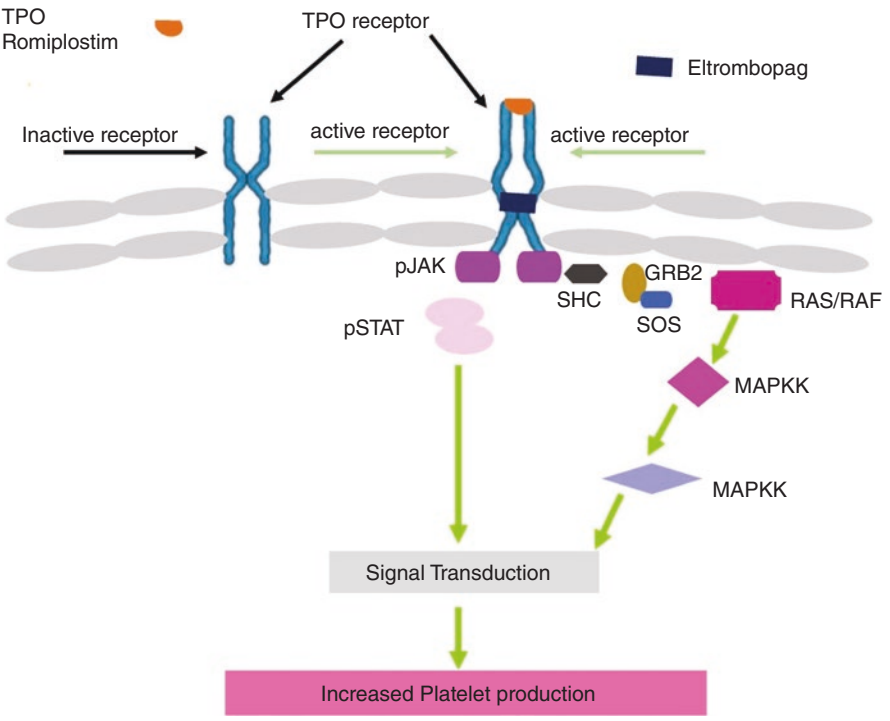

Fig. 1.3 Cellular mechanism action of Thrombopoietin Receptor Agonists (TPO-RA): Romiplostim and Eltrombopag are TPO agonists that bind to the TPO receptor and activate the JAK-STAT and MAPK signaling pathway, which induces the transcription of upstream genes of the platelet production. This leads to increased platelet production

acid peptides, approved in August 22, 2008 by FDA for long-term treatment for chronic ITP in adults who have not responded to other treatments. Along with rhTPO, the application of these molecules in CIT and RIT shall be discussed in the following sections.

1.7 Explore the Other Causes: Every Case of Thrombocytopenia in Chemotherapy Recipients are not due to Chemotherapy Alone

(a) Is there an associated immune thrombocytopenia or coagulopathy? Or is disease itself causing thrombocytopenia?
(b) Has the patient been introduced a newer medication recently? Has there been a recent infection or transfusion?
(c) Is there a chemotherapy- or disease-related thrombotic microangiopathy?
(d) Is the thrombocytopenia temporally related to radiation therapy?
(e) What dose and type of chemotherapy were given? Also what was the gap between the 2 cycles?

1.8 The Recent Recommended Approaches for CIT and RIT

There are many guidelines or algorithm available for treatment of thrombocytopenia. However, data is limited for treatment of the same condition induced by chemotherapy or radiotherapy (CIT and RIT). It depends on intent of the underlying treatment for a particular patient. Firstly, risk assessment for bleeding complications and the goal of treatment needs to be defined upfront (curative or palliative approach). Risk assessment is much emphasised when the patients are on anticoagulant therapy, or any other therapy related to the co-morbidity condition of the patient.

- For immediate recovery, platelet transfusion is necessary. Single donor platelets (SDP) are recommended compared to random donor platelets (RDP) for faster and sustained increment. This is more beneficial in patients of hematological malignancies undergoing chemotherapy or patients with severe aplastic anemia (SAA) who are in a state of bridge to transplantation.
- Rationalise the chemo regimen or dose of individual agent particularly those having more of myelosuppressive property
- Treat any other causes of thrombocytopenia: like rationalise the antibiotics if patient is on sepsis and receiving multiple antibiotics. For example, linezolid has been shown to cause myelosuppression, hence needs to be avoided [15].
- Look for coagulopathy judiciously and if any present, then treat them proactively. The data shows some tumors like adenocarcinoma of pancreas and gastric origin can cause chronic disseminated intravascular coagulation.

- To improve the haemostasis, various ant fibrinolytic agents like epsilon-aminocaproic acid (EACA) or Tranexamic acid (TXA) have been used. Tranexamic acid doses of 4–6 g per day in divided doses 6–8 h have been used in adults. However, these anti-fibrinolytic agents should be used cautiously as they increase the risk of thrombosis at the same time. National Comprehensive Cancer care Network (NCCN) recommend holding antifibrinolytics when endogenous platelet counts are >30 K/mcL and in patients with embolic strokes, active thromboembolism, and urinary tract bleeding [16].
- Recently, TPO-RA use is endorsed by NCCN, for the treatment of CIT. TPO, also known as c-Mpl ligand, is a relatively lineage-specific cytokine that stimulates megakaryocyte growth and maturation in vitro and is also a potent in vivo thrombopoietic growth factor which promotes megakaryocyte differentiation from hematopoietic stem cells and increases production of platelets.
- PF4 inhibition may have role in the condition which is associated with increased intra-marrow turnover of megakaryocytes such as RIT and CIT and also in ITP and MDS.

1.8.1 Treatment of Chemotherapy Induced Thrombocytopenia (CIT)

The clinical studies in the earlier days was done employing different cytokines, including IL-1, IL-3,IL-6, and IL-11, which showed their definite ability to stimulate platelet production either directly or indirectly in patients with CIT. However, its use is very limited because of side effects. Later the TPO molecules have shown clinical relevance. Following are few of the published data on use of these molecules in CIT.

1.8.2 Treatment with PEG-rhMGDF and rhTPO

In a major study by Basser et al. on 68 patients with advanced malignancy, who were treated with intravenous carboplatin 600 mg/m^2 and cyclophosphamide 1200 mg/m^2 and filgrastim 5 μg/kg/day in their first cycle [17]. In further cycles they received, additionally PEG-rhMGDF for 1, 3 or 7 days after chemotherapy. Patients showed a significantly higher platelet nadir with addition of study drug compared to cycle 1, (47.5×10^9/L vs. 36×10^9/L; $P = 0.003$). Not only the count but the duration days of grade 3 or 4 thrombocytopenia was also significantly shorter (0 vs. 3 days; $P = 0.004$) and no difference in the time of platelet recovery was observed. In another study done by Fanucchi et.al, PEG-rhMGDF was administration after treatment of lung cancer patients with carboplatin and paclitaxel for up to 16 days [18]. They found rise in platelet counts was statistically significant compared to placebo group. The median platelet count was 188×10^9/L *versus* 111×10^9/L ($p = 0.013$) in the study and placebo group respectively. Not only the number but duration of persistence was also increased from 7 days to 15 days ($P < 0.001$). The platelet count

recovered to baseline in 14 days in the patients given PEG-rhMGDF, as compared with more than 21 days in those receiving placebo ($P < 0.001$). Neither the incidence of thrombosis was increased nor the survival affected. Another study by Moskowitz et al., in 2007 on 41 patients with Non-Hodgkin's lymphoma treated with ICE protocol has shown survival benefit from 21% to 31% ($p = 0.06$) after a median follow up of 8.6 years when they treated with PEG-rhMGDF [19].

Most important question is when to start, whether pre or post chemotherapy, with first or subsequent cycle and at what doses? A study at MD Anderson by Raj VS et al., in 2000 on 29 patients with gynaecologic cancer with rhTPO have shown a significantly reduced degree and duration of thrombocytopenia and enhanced platelet recovery after the administration of rhTPO days 2, 4, 6, and 8 after chemotherapy [20]. In patients who received the optimal biological dose of rhTPO (1.2 μg/kg of body weight) in cycle 2 (carboplatin plus rhTPO), the mean platelet count nadir was higher (44×10^9 cells/L and 20×10^9 cells/L; $P = 0.002$) and the duration of thrombocytopenia was shorter (days with a platelet count $<20 \times 10^9$ cells/L, 1 and 4 days [$P = 0.002$]. The need for platelet transfusion in this group was reduced from 75% of patients in cycle 1 to 25% of patients in cycle 2 ($P = 0.013$).

Although rhTPO is approved for CIT in China, and the numerous studies showed a definitive benefit in platelet count with the intervention compared to placebo, it is hard to assess from the published data as to whether any clinical endpoints such as relative dose intensity, remission rate, bleeding or any adverse events or survival were impacted.

1.8.3 Treatment of CIT with Newer TPO-RA

In a study performed at Memorial Sloan–Kettering Cancer Center from 2010–2012 on cancer patient, who already had persistent thrombocytopenia post chemotherapy were treated with 1–2 mg/kg of romiplostim weekly throughout the chemotherapy [21]. The platelet counts improved in all and 19/20 had platelet counts of 100×10^9/L or more. Three out of 20 patients developed deep vein thrombosis (DVT).

Another phase-II randomized prospective trial in solid tumour patients with CIT, conducted by Soff GA et al., in patients with mean platelet counts 62,000/μL for at least 4 weeks despite dose reduction or delay of chemotherapy [22]. In the randomization phase, 14 of 15 romiplostim-treated patients (93%) experienced correction of their platelet count within 3 weeks, compared with one of eight control patients (12.5%; $P < .001$). Including all romiplostim-treated patients ($N = 52$), the mean platelet count at 2 weeks of treatment was 141,000/μL compared to 57,000/μL in observation group. Forty-four patients who achieved platelet correction with romiplostim resumed chemotherapy with weekly romiplostim. Only 6.8% patient experienced recurrent reduction or delay of chemotherapy because of isolated CIT. They concluded that Romiplostim is effective in correcting CIT, and its maintenance prevents further delay in chemotherapy or any recurrence of CIT in most patients. Twenty-eight patients were continued on romiplostim for more than 6 months at a mean dose of 3.3 μg/kg. The incidence of venous thromboembolism (VTE) was

10.2% during the first year of romiplostim therapy with none discontinuing romiplostim.

In a report from four Boston cancer centers over 10 years, romiplostim had been utilized for CIT patients as a supportive care [23]. The patients who had a platelet count below 100×10^9/L for at least 3 weeks after their last chemotherapy treatment or a dose delay of longer than 1 week were enrolled. A total of 173 CIT patients (153 with solid tumors, 20 with lymphoma or myeloma) were treated. Approximately 90% received median of 4 cycles (range, 1–30) of chemotherapy on romiplostim. Amongst all the solid tumor patients, 71% had a platelet response, 79% avoided dose reductions/ delays of chemotherapy and 89% did not require platelet transfusion. The median baseline rise in the platelet count was statistically significant, $p = 0.001$ (116×10^9/L Vs 60×10^9/L ($P = 0.001$). The median weekly romiplostim dose was 3 mg/kg (interquartile range, 3–5 mg/kg). Patients who had extensive bone marrow involvement by tumor, prior pelvic radiotherapy or treated with temozolomide failed to show the response. Also response rate was lower in patients with aggressive lymphoma and myeloma. The incidence of adverse event like thrombosis was observed in 11% and bleeding rates 7.1%. In this study 2 different dosing algorithms were explored: (1) On days of chemotherapy administration (2) except on days of chemotherapy administration along with weekly doses. Patients on weekly dosing had a significantly higher median platelet count (143×10^9/L vs. 106×10^9/L; $P < 0.001$) and a higher rate of achieving a platelet response (81% vs. 63%; $P = 0.006$). Other clinical out-comes including the extent of chemotherapy RDI reduction and bleeding were better in patients receiving weekly treatment. The two ongoing trials of romiplostim in CIT are, NCT03937154 and NCT03362177.

In a randomized study (NCT00102726) on prophylaxis in 183 patients with CIT, receiving either placebo or eltrombopag with various doses 50 mg, 75 mg or 100 mg on days 2 through 11 for at least two 21-day chemotherapy cycles [24]. No toxicity was observed with eltrombopag, and it increased the platelet count in CIT compared to placebo group. Various other studies have documented the beneficial effects of eltrombopag and the maximum tolerated dose was capped at 100 mg due to the risk of thrombo-embolic events [3/183]. A larger randomised phase II study investigated eltrombopag 100 mg as prophylaxis for the prevention of CIT in patients receiving either gemcitabine alone (42 patients) or gemcitabine with carboplatin or cisplatin (32 patients) over six cycles of chemotherapy. The primary endpoint was the mean pre-treatment platelet count over six cycles of chemotherapy. The treatment was well tolerated with no increased risk of thrombosis (5/52 [9.6%] on eltrombopag and 2/23 [8.7%] on placebo) but was complicated by a 65% withdrawal rate. The geometric mean platelet count of the 48 eltrombopag–treated patients was 246×10^9/L compared with 193×10^9/L for the 23 placebo patients, but the difference did not attain statistical significance ($p = 0.103$). Patients receiving eltrombopag had a slightly lower rate of grade 3/4 thrombocytopenia (27/50 [54%] vs. 16/23 [70%]) and slightly higher nadir platelet counts than patients receiving placebo.

Zhu et al., carried out a real-world retrospective observational study in China, regarding the assessment of the response in lymphoma patients whose platelet

counts dropped below 30×10^9/L and who were then treated with eltrombopag ($n = 51$), rhTPO ($n = 50$) or no platelet growth factor support ($n = 52$) [25]. The baseline platelet counts were 24×10^9/L in all three groups. After 10 days, the platelet count [median (standard division)] in those on eltrombopag and rhTPO was higher compared to placebo patients (131×10^9/L [71×10^9/L], 147×10^9/L [68×10^9/L], and 76×10^9/L [40×10^9/L] (in placebo group), respectively; $P < 0.001$). In this study the period [mean days (Standard deviation)] of thrombocytopenia (platelet counts $<50 \times 10^9$/L) was 6.25 (2.61), 5.48 (2.62), and 8.33 (3.98) days, respectively ($P = 0.036$). The days [mean days (standard deviation)] required for recovery of platelet counts to more than 50×10^9/L was 6.33 (2.31), 5.44 (2.57), and 8.32 (2.53) days, respectively in eltrombopag, rhTPO and placebo groups ($P = 0.001$). Patients receiving eltrombopag or rhTPO were less likely to have grade 2/3 bleeding (5.9% and 4.0%) compared with untreated patients (11.5%). Many other studies are currently ongoing.

1.8.4 Other Drugs in the Pipeline

Avatrombopag has been studied in patients with CIT with solid organ malignancies but failed to show any benefit. Several CIT studies are ongoing with Avatrmbopag. Another molecule under study is Hetrombopag for which ongoing study is: NCT03976882: A Randomized, Double-blind, Placebo-controlled Multi-centre Study with an Open-label Extension to Evaluate the Efficacy and Safety of Hetrombopag for the Treatment of Chemotherapy-induced Thrombocytopenia in subjects with malignancy.

1.9 Conclusions

Thrombocytopenia is a common hematological complication developing following chemotherapy and radiotherapy in patients with malignancies, both hematological as well as non-hematological. This is one of known risk factor for bleeding and a serious obstacle to maintenance of dose intensity of chemotherapy regimens, compromising the therapeutic effect and ultimately the overall response. Oncologists should focus on addressing risk factors for thrombocytopenia, both in terms of preventing severe bleeding complications as well as maintain unhindered cancer-directed therapy. Platelet transfusion remains the cornerstone for acute management of thrombocytopenia in cancer. Novel agents like TPO-RA have shown beneficial effect in both CIT and RIT. In addition, whether a TPO plus anti-PF4 strategy can be developed to improve the outcomes in RIT remains to be seen.

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1. CIT frequently complicates cancer treatment causing delays in chemotherapy treatment, dose reductions, and discontinuation, ultimately compromising the outcomes.
2. Single donor platelet (SDP) transfusion is most effective way to prevent the acute complications due to thrombocytopenia.
3. Romiplostim (TPO-RA) is effective for the management of CIT in patients with solid tumors, as demonstrated by early recovery of platelet counts and low rates of chemotherapy dose reductions, treatment delays, bleeding, and platelet transfusions.
4. Romiplostim weekly dosing resulted in improved outcomes as compared with more intermittent intracycle dosing.
5. Romiplostim was generally ineffective in patients with BM invasion by tumour, prior pelvic irradiation or on temozolomide.
6. VTE is one of important side effect related to use of TPO-RA which should be looked for once patient is on continuous exposure.
7. Clinical development of rhTPO and PEG-rhMGDF has stopped in 2000 due to the development of neutralizing antibodies to PEG-rhMGDF.
8. The rhTPO is widely used to treat CIT in China and is unavailable elsewhere.
9. Eltrombopag is also approved and its dose is capped to 100 mg once daily for CIT and RIT.
10. The Clinical practice guidelines need to be followed for specific clinical circumstances with full understanding of overall condition of individual patient.

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Management of Radiation Proctitis

2

Vineeta Goel and Rachna Jain

2.1 What Is Radiation Proctitis?

Radiation proctitis is inflammation of the rectum that occurs as a result of acute damage to the rectum sustained from secondary to pelvic radiation therapy. Pelvic radiotherapy is an essential component of treatment for many pelvic malignancies—urological, gynaecological, and gastrointestinal malignancies (prostate, urinary bladder, cervix, uterus, and anus). During the course of pelvic radiotherapy, the rectum may be damaged, as it lies within the field of irradiation.

2.2 Types of Radiation Proctitis

Radiation proctitis can be classified as acute or chronic, depending upon the time duration of symptoms in relation to the treatment.

- Acute Radiation Proctitis - It occurs within six weeks of radiation therapy.
- Chronic Radiation Proctitis (CRP)—It may either occur as a sequel of acute radiation proctitis or may have a delayed inception (10-15 months to 30 years after radiation exposure) [1].

2.3 Incidence

Incidence of Acute Radiation Proctitis—The incidence of acute radiation proctitis is in the range from 8% to 13% when treated with brachytherapy alone and up to 21% when used in combination with other modalities [2].

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Incidence of Chronic Radiation Proctitis (CRP)—It is a relatively frequent late (after 3–6 months) side effect that affects 5–20% of cancer patients [3].

2.4 Risk Factors

Risk factors for radiation proctitis depends upon the volume of rectum irradiated, RT technique, total RT dose, and dose per fraction [4].

- Doses of radiation <45 Gy can cause lesser radiation proctitis.
- Doses between 45 and 70 Gy cause higher incidence of proctitis.
- Doses above 70 Gy causes significant injury to the surrounding area [5, 6].

Incidence of radiation proctitis is lesser with more conformal form of radiation techniques like IMRT, VMAT, IGRT as compared to 3 DCRT or conventional form of RT.

Factors which can increase the susceptibility to Radiation Proctitis [7, 8]:

- Coexisting vascular disease
- Connective tissue disease
- Inflammatory bowel disease
- Concomitant chemotherapy
- Smoking and alcohol
- Diabetes

2.5 Pathogenesis

Ionizing radiation can cause acute and chronic damage to normal rectum and colon. Proctitis manifests as vascular damage, mucosal ischaemia, thickening and ulceration. CRP occurs due to progressive epithelial atrophy and fibrosis associated with obliterative endarteritis, chronic mucosal ischemia, submucosal fibrosis, and new vessel formation, which leads to clinical symptoms [9] such as bleeding, ulcers, strictures and fistula formation. CRP is also termed as Radiation Associated Vascular Ectasias (RAVE) for cases where bleeding occurs from vascular ectasias, rather than ischemia and fibrosis [10].

2.6 Symptoms

Acute proctitis symptoms—diarrhea, mucus discharge, urgency, tenesmus, and uncommonly bleeding [7].

Chronic radiation proctitis—diarrhea, mucus discharge, urgency, tenesmus, and bleeding with potential iron-deficiency anemia that requires blood transfusions, obstructed defecation due to strictures with symptoms of constipation, rectal pain, urgency, and, rarely, fecal incontinence due to overflow [7].

2.7 Diagnosis

Diagnosis by endoscopy (colonoscopy or sigmoidoscopy) is important to exclude other causes of proctitis (inflammatory bowel disease, infectious colitis, ischemic colitis, diversion colitis, diverticular colitis) [11]. Figure 2.1 depicts the endoscopic findings.

There are three main forms of endoscopic findings in CRP:

- Inflammation predominant form (I-CRP)—edema, mucosal pallor, and ulcer
- Bleeding predominant form (B-CRP)—friability, spontaneous hemorrhage, and telangiectasia
- Mixed form—with features from both I-CRP and B-CRP [11].

Vienna Rectoscopy Score (VRS) is used for the endoscopic classification of CRP and is used to describe rectal mucosa [12]. The VRS divides the inner rectal mucosa into 12 mucosal areas.

Scoring of VRS: Each area is scored on the presence and grading of

- Telangiectasia (Grade 0–3)
- Congested mucosa (Grade 0–3)
- Ulceration (Grade 0–4)
- Stricture (Grade 0–4)
- Necrosis (Grade 0–1)

2.7.1 Role of Biopsies in Radiation Proctitis

When suspecting radiation proctitis, rectal biopsies are contraindicated as they may initiate chronic, poorly healing wounds and increase risk of rectal fistulas. Biopsy is justified only if a malignancy is suspected. Biopsies should be taken from the

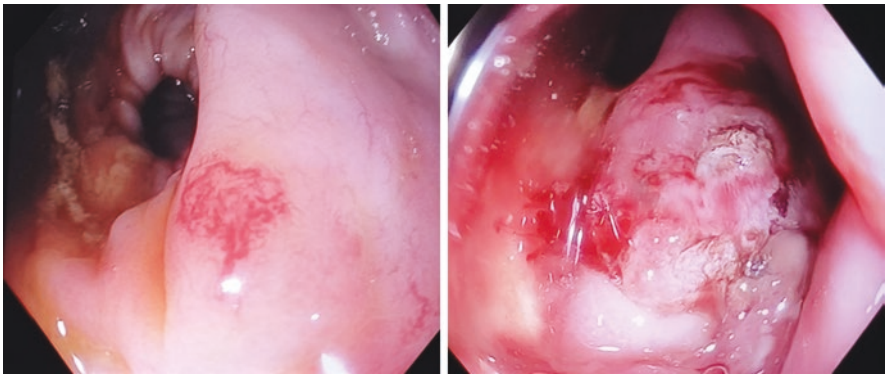

Fig. 2.1 Endoscopic features illustrating oedema, telangiectatic lesions and ulcers