Review

Hematological Changes Following Low Dose Radiation Therapy and Comparison to Current Standard of Care Cancer Treatments

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Abstract

Cancer is the second leading cause of mortality worldwide accounting for almost 10 million deaths in 2020. Current standard of care treatment varies depending on the type and stage of disease, but commonly includes surgery, chemotherapy, and/or radiation therapy. There is evidence that whole- and half-body exposure to low dose ionizing radiation can also be an effective therapeutic due to its stimulation of anti-cancer immunity. One of the limiting factors for past clinical trials using low dose radiation therapy has been adverse hematological events. However, similar hematological changes are also frequently reported following standard of care treatments in oncology. This review summarizes the effects of various cancer therapies on hematologic toxicity through the evaluation of complete blood count reports. The reviewed literature elucidates hematological trends in patients undergoing chemotherapy, and both high and low dose radiation therapy. In general, high dose radiation and chemotherapy can result in widespread changes in blood counts, with the most severe effects related to leukopenia. Overall, compared to standard of care treatments, low dose radiation results in similar, yet more mild hematological changes. Taken together, hematological toxicities should not be a limiting factor in the applicability of low dose radiation as a cancer therapeutic.

Keywords

cancer therapy, complete blood count, hematology, low dose radiation

Introduction

It is estimated that over 19 million new cases of cancer were diagnosed worldwide in 2020 with a mortality rate of nearly 10 million.[1] In the United States alone, an estimated 1 806 590 cancer cases were diagnosed in 2020 resulting in a mortality rate of 606 520, representing the second most common cause of death.[1] Additionally, in Canada, cancer is the leading cause of death and it is predicted that 1 in 2 Canadians will be diagnosed in their lifetime.[2] With increasing success in screening programs and continued development in treatment options, there is currently a 63% 5-year survival for all cancer types, which is a promising increase from a 55% 5 year survival rate in 1994.[2]

Despite an increase in both the number and quality of cancer therapies over the last decade, managing a cancer diagnosis still poses high symptom burden on patients. When considering a treatment plan, patients are faced with decision factors including treatment efficacy, overall survival, and changes in quality-of-life during and after the treatment has finished. New cancer therapies are continuously being explored to improve the quality-of-life of patients during their cancer diagnosis. One option that has been explored and

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associated with minimal side effects, is low dose radiation therapy (LD-RT). LD-RT is a non-targeted approach to radiation that, when delivered over a half-body or full-body field, can be an effective cancer therapeutic. This option was explored readily in the 1960s and 1970s until the widespread use of chemotherapeutics, and since then has been declining in use. Despite this decline, LD-RT has shown clinical success rates comparable or better to conventional cancer therapies. To date, LD-RT clinical trials have identified some potential hematological toxicities associated with these treatments, which could be another reason for the decline in use; however, the risk factor associated with these effects have not been well documented compared to current standard of care.

The reproduction of blood cells is one of the most radio- and chemo-sensitive process in the body and acute bone marrow suppression is often seen as a dose limiting side effect in both radiation and chemotherapy. Suppression of blood cell counts can lead to many adverse side effects that can cause conditions requiring medical attention, the need for hospitalization, or even death. Depending on the type of blood cell primarily being affected, anemia, leukopenia, and thrombocytopenia can occur. This review explores the hematological effects of current cancer treatments by standard clinical complete blood count (CBC) reports. The literature reviewed focuses on the hematological effects of LD-RT alongside common conventional cancer treatments—high dose radiation therapy (HD-RT), chemotherapy, and chemoradiation. Studies were evaluated by their descriptions of cancer type and treatment regime along with the presence of one or more blood count parameters.

Blood Components

Hematopoiesis is the production of new circulating cells in the blood and occurs in order to replenish the circulatory system to maintain steady state concentrations. The process begins in the bone marrow where hematopoietic stem cells differentiate into erythrocytes (red blood cells; RBCs), leukocytes (white blood cells; WBCs), and thrombocytes (platelets).[3-6] Specific details on the process of hematopoiesis have been covered in various review articles.[3-5] Erythrocytes carry oxygen to tissues in the body, and in return bring carbon dioxide back to the lungs as waste. Low erythrocyte levels can cause anemia which occurs when there is insufficient oxygen distributed to body tissues, and can cause symptoms such as fatigue, weakness, paleness, dizziness, shortness of breath, or increased heart rate.[6] Leukocytes are the bodies primary defense against infections and foreign materials in the body. Patients with a low leukocyte count (leukopenia) have an increased susceptibility to infection. There are various types of leukocytes which are broadly divided based on their myeloid (monocytes, neutrophils, basophils, and eosinophils) or lymphoid (lymphocytes) lineage.[6] Finally, thrombocytes are responsible for blood clotting to avoid patient hemorrhages or excessive bleeding. Symptoms of low thrombocytes (thrombocytopenia) can include excessive bruising or internal bleeding often reported as blood in the urine or stool.[6]

Complete blood count reports are a tool used clinically to measure the levels and types of circulating blood components.[6] In cancer patients, a physician will use CBC reports to help diagnose disease, as well as monitor response and tolerability to treatment. Evaluation of erythrocyte levels and its related measures, such as hemoglobin and hematocrit can give insight into the patients' oxygen-carrying capacity. Alternatively, leukocyte measurements on the CBC can provide information regarding overall immune function.

When the number, size, and maturity of each of these types of blood cells deviate from normal values, it can signify infection or disease. As a result, several different metrics have been designed to quantify how to measure for hematologic toxicity in patients. These include the World Health Organization (WHO) Toxicology Grades,[7] the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE),[8] toxicity and response criteria of the Eastern Cooperative Oncology group (ECOG),[9] and the Southwest Oncology Group (SWOG) toxicity criteria,[10] which are summarized in Table 1.

Cancer Therapies

Standard of Care. Multiple treatment options for cancer are available, including surgery, chemotherapy, radiation therapy, immunotherapy, targeted therapy, and hormone therapy. This review will focus on the hematological effects observed with the 2 main non-surgical therapeutics—chemotherapy and radiation therapy—but it is important to understand how all of these routes of therapy are often sought out in combination to better the odds of patient survival.

Surgery plays an important role in cancer management, whether the aim is to completely remove a tumor mass (resection) or to make it smaller (debulking). The goal of surgery in the management of cancer is to remove as much of the involved tissue as possible while still allowing for normal, or close to normal organ function.[11] The ideal outcome of surgery is complete resection with negative margins, meaning there is no cancerous tissue left behind.[11] There are many instances where surgery is not a viable option as it would impair normal function too drastically, such as oral or anal cancers, or there is not a solid tumor mass to remove (i.e., blood born cancers).

Chemotherapy uses cytotoxic drugs to kill cancer cells in the body. Chemotherapy is generally a systemic treatment that non-specifically targets any rapidly dividing cells.[11] This lack of specificity results in damage to normal tissues and often leads to side effects. Chemotherapy can be given alone but is often given in combination with other treatment modalities. For example, chemotherapy can be given before surgery in attempt to shrink tumors, or after surgery to target any remaining microscopic cancer cells.[11] Depending on the cancer type, the standard of care is to have concurrent chemoradiation

Table 1. Summary of Hematological Toxicity Scales Developed by the World Health Organization (WHO), National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE), Eastern Cooperative Oncology group (ECOG), and Southwest Oncology Group (SWOG).

Metric	Grade				
	0	1	2	3	4
WHO					
Leukocytes (x10^3 cells/μL)	>4.0	3.9–3.0	2.9–2.0	1.9–1.0	<1.0
Granulocytes (x10^3 cells/μL)	>2.0	1.9–1.5	1.4–1.0	.9–0.5	<0.5
Thrombocytes (x10^3 cells/μL)	>100	99–75	74–50	49–25	<25
Hemoglobin (g/dL)	>11.0	10.9–9.5	9.4–8.0	7.9–6.5	<6.5
CTCAE					
Leukocytes (x10^3 cells/μL)	WNL	<LLN–3.0	<3.0–2.0	<2.0–1.0	<1.0
Granulocytes (x10^3 cells/μL)	WNL	<LLN–1.5	<1.5–1.0	<1.0–0.5	<0.5
Lymphocytes (x10^3 cells/μL)	WNL	<LLN–0.8	<.8–0.5	<.5–0.2	<0.2
Thrombocytes (x10^3 cells/μL)	WNL	<LLN–75	<75–50	<50–25	<25
Hemoglobin (g/dL)	WNL	<LLN-10.0	<10.0-8.0	<8.0	
ECOG					
Leukocytes (x10^3 cells/μL)	≥4.5	<4.5–3.0	<3.0–2.0	<2.0–1.0	<1.0
Granulocytes (x10^3 cells/μL)	≥1.9	<1.9–1.5	<1.5–1.0	<1.0–0.5	<0.5
Thrombocytes (x10^3 cells/μL)	≥130	<130–90	<90–50	<50–25	<25
Hemoglobin (g/dL)	≥11	10.9–9.5	<9.5		
Hematocrit (%)	≥32	31.9–28	<28		
SWOG					
Leukocytes (x10^3 cells/μL)	≥4.0	3.9–3.0	2.9–2.0	1.9–1.0	<1.0
Granulocytes (x10^3 cells/μL)	≥2.0	1.9–1.5	1.4–1.0	.9–0.5	<0.5
Lymphocytes (x10^3 cells/μL)	≥2.0	1.9–1.5	1.4–1.0	.9–0.5	<0.5
Thrombocytes (x10^3 cells/μL)	WNL	Normal–75.0	74.9–50.0	49.9–25.0	<25.0
Hemoglobin (g/dL)	WNL	Normal–10.0	9.9–8.0	7.9–6.5	<6.5

WNL = within normal limits, LLN = lower limit of normal. Table only summarizes metrics that are relevant to the studies that were reviewed and was produced based on data from.[7-10]

with or without adjuvant surgery. For example, patients with anal or rectal cancer will have chemoradiation before surgery is performed to try and preserve the sphincter. For patients with brain tumors such as glioblastoma multiforme, surgery will be performed first, followed by radiation to the tumor bed with concurrent chemotherapy using temozolomide, which is one of few agents that can cross the blood brain barrier. Since chemotherapy is a systemic treatment, it travels throughout the entire body making it effective for treating metastatic disease. However, some cancers have a poor response rate to chemotherapy. For instance, chemotherapy generally plays a small role in the treatment of prostate cancer, but it can be used to manage disease that has metastasized outside of the prostate, that is not responsive to hormone therapy, or that has recurred.[11]

There are 2 general forms of high dose, or conventional, radiation therapy; external beam radiation therapy (EBRT) and internal radiation therapy which can be administered using sealed sources (brachytherapy) or unsealed sources (e.g., radioiodine therapy). Radiation therapy can be used alone or with other modalities to treat cancer, or in a palliative setting to relieve symptoms. A patient may receive HD-RT before surgery to shrink a tumor to increase the odds of complete resection. Alternatively, it can be given after surgery if there is evidence that microscopic disease remains in or around the surgical site. It is also common for radiation to be delivered to a tumor bed as the standard of care, specifically for breast cancer or brain tumors, to reduce the risk of recurrence. Finally, if the cancer is advanced radiation can be used to control the disease and relieve patient symptoms either from their primary tumor or metastases. Internal therapy may be given in combination with EBRT to boost dose to a tumor.

LD-RT. Although radiation therapy is generally performed with high doses targeted to a localized region, there has recently been a resurgence in interest in the effects of EBRT in much lower doses. In animal models, these very low sublethal doses have been shown to not only delay primary tumor growth[12,13] but ultimately suppress distant metastatic lesions.[14,15] In humans, LD-RT was first used to treat cancer over 50 years ago.[16] To date the majority of human clinical trials has focused on patients with hematological malignancies.

The aim of conventional HD-RT is to deliver targeted radiation treatments to a tumor in order to selectively kill cells within a particular treatment field. However, exposure to

LD-RT is known to have different cellular and molecular effects compared to HD-RT. In general, low doses of radiation have been shown to activate cellular defenses capable of repairing DNA damage, remove cells via autophagy and apoptosis that are unable to be repaired, activate cell cycle arrest preventing damaged cells from dividing and allowing for repair, and induce adaptive memory offering defense against future oxidative stress.[17] With respect to cancer therapy, LD-RT is thought to target cancer phenotypes indirectly through a systemic enhancement of the immune system.[18] Although the full mechanism remains unknown, key drivers of LD-RT anticancer immunity include a stimulation of cancer suppressing cell types, such as natural killer cells and cytotoxic T cells, as well as a suppression of cancer promoting cells such as regulatory T cells.[19-21] Various cytokines and chemokines, including interferon gamma and interleukin 2, have also been implicated in the mechanism of LD-RT.[22]

Treatments using LD-RT generally use total doses of 1–2.5 Gy, delivered over the span of several weeks in fractions of 5–20 cGy, delivered over whole-body or half-body fields. Data from human clinical trials suggests that LD-RT is equally effective compared to other standard of care treatments. For example, individuals receiving LD-RT showed a complete response which was comparable to patients treated with multi-agent chemotherapy.[23,24] In some cases, overall survival was significantly greater in patients receiving LD-RT compared to standard chemotherapy.[25] A major benefit to LD-RT is the reduction of reported side effects compared to chemotherapy and HD-RT. However, there has been apprehension surrounding the large size of these treatment fields and how this might affect blood counts if a large amount of the body is being irradiated, even at low doses. At the same time though, while the effects of LD-RT on the hematologic system are thought of as a potentially limiting factor due to the volume being irradiated, changes in hematologic parameters are nothing new in the world of cancer therapy.

The goal of this review is to uncover trends in hematologic toxicity induced by cancer management in efforts to elucidate how the hematologic system responds to the cytotoxicity of cancer treatments. In addition, this review seeks to compare evidence from clinical use of non-targeted LD-RT to current treatment options for metastatic cancers to determine if LD-RT would have less adverse advents compared to standard practice. The literature reviewed focuses on CBC data from the most common cancer treatments including radiation therapy, chemotherapy, and combined chemoradiation therapy, with an emphasis on the use of LD-RT.

To compile the collection of papers to include in this review, searches were conducted using PubMed. An initial search was conducted using the terms “radiation therapy/radiotherapy” or “chemotherapy.” The initial list was further refined using the terms “hematological toxicity” and “complete blood count.” Publications on LD-RT date back to the 1970s. To ensure that these studies were included in the review, a date range of 1970–2020 was applied to the search. The list of publications was then evaluated for the following inclusion criteria: (1) full articles were available and were in peer reviewed journals, (2) articles were in English, (3) articles included a detailed description of treatments (i.e., chemotherapy drug and dose, radiotherapy dose and fractionation regimen, etc.), and (4) some data was presented on blood cell counts (although articles did not have to include full CBC data). The final list was then compiled into 4 categories: LD-RT, HD-RT, chemotherapy, and chemoradiation. A total of 12 papers were included for LD-RT, 10 for HD-RT, 14 for chemotherapy, and 12 for chemoradiation A summary of these papers is outlined in Table 2.

Hematological Effects

LD-RT. Human clinical trials involving whole- or half-body LD-RT began in the late 1960s through the 1970s with the work by Johnson[26-28] on non-Hodgkin’s lymphoma (NHL) and chronic lymphocytic leukemia (CLL). Treatments for NHL with total body irradiation (TBI) mildly affected hematologic status, but severely low blood counts did not occur in these studies.[27,28] In patients treated for CLL with TBI of 3–10 cGy/fraction in 3–5 fractions/week (100–400 cGy total), 5% experienced some degree of anemia, and 15% some degree of thrombocytopenia, but treatment interruption coupled with corticosteroids allowed for quick recovery of these mild hematologic toxicities.[28]

After seeing encouraging results by Johnson, Chaffey et al[29] used TBI to treat 64 patients with lymphosarcoma with total doses ranging from 15 to 210 cGy. All treatments were performed in 2 fractions per week for 5 weeks. Thrombocytopenia occurred to some degree in all patients causing treatment to be temporarily interrupted in over one third of participants. Forty percent of patients developed thrombocytopenia of $<40x10^3/\mu L$ shortly after treatment was completed, but these counts returned to normal levels soon after. Thrombocytopenia was the only significant toxicity although leukocytes and erythrocytes were also mildly depressed. Thrombocytopenia was also reported as the main toxicity by Mendenhall et al,[30] who treated 60 patients with advanced NHL using TBI between 1972 and 1977. Two different treatment regiments were used. Regimen A consisted of 10 cGy/fraction, 5 fractions/week for 2–3 weeks, while regimen B consisted of 15 cGy/fraction twice a week for 5 weeks. Thrombocytopenia was reported; however, only 34% of patients had their platelet counts fall below $50x10^3/\mu L$. Other complications apart from thrombocytopenia included the need for blood transfusions in 8 patients, bleeding in 3 patients, and one patient went septic. No deaths related to LD-RT occurred.

In addition to thrombocytopenia, several studies also reported reductions in leukocytes. Lybeert et al[31] examined 68 patients treated from 1973 to 1979, the majority with advanced NHL. Patients were treated with TBI of 10 cGy/fraction, 3 fractions/week to a total dose of 180–220 cGy. Hematologic toxicity was limited to thrombocytopenia and leukopenia.

Table 2. Summary of Hematological Changes Following LD-RT, HD-RT, Chemotherapy, and Chemoradiation.

		Hematological toxicities			
Cancer type	Dose/fractionation regimen	Leukocytes	Thrombocytes	Erythrocytes/ hemoglobin	Reference
LD-RT					
CLL	TBI of 3–10 cGy/fraction, 3–5 fractions/week, 100–400 cGy total		Thrombocytopenia in 15%	Anemia in 5%	Johnson[28]
Lympho-sarcoma	TBI of 15–210 cGy in 2 fractions/week for 5 weeks	Mildly depressed	Occurred to some degree in all patients, treatment interruption in 1/3	Mildly depressed	Chaffey et al[29]
NHL	Regimen A: TBI of 10 cGy/fraction, 5 fractions/week for 2–3 weeks Regimen B: TBI of 15 cGy/fraction twice a week for 5 weeks		Thrombocytopenia in 34%		Mendenhall et al[30]
NHL	TBI of 10 cGy/fraction, 3 fractions/week, 180–220 cGy total	Average increase in grade of 2.2 (WHO) 3% grade 1 6% grade 2	Average increase in grade of 2.1 (WHO) 1 patient grade 3		Lybeert et al[31]
NHL	Two cycles of TBI in 4 20 cGy fractions, 160 cGy total	<3.9x10^3 cells/μL in 45.7%	<100x10^3 cells/μL in 54.3% <50x10^3/μL in 73.7% 71.4% requiring platelet transfusion	Hemoglobin <10 g/dL in 20%	Safwat et al[32]
Advanced NHL	Two TBI treatment schedules, 150 cGy total	Median nadir of 3.7x10^3 cells/μL	Median nadir of 77x10^3 cells/μL		Choi et al[33]
Advanced lymphoma	TBI of 150 cGy total in 2–3 fractions/week	<2x10^3 cells/μL in 17.6%	<50x10^3 cells/μL in 17.6%		Hoppe et al[25]
Low-grade NHL	TBI of 10 cGy/fractions, 3 fractions/week, 250 cGy total	44% of patients developed grade 3 (WHO) toxicity and 16% grade 4			Meerwaldt et al[23]
Advanced lymph ocytic lymphoma	TBI of 10 cGy/fraction for 5 weeks, 150 cGy total	Severe or life-threatening granulocytopenia in 73% patients One death due to infection	Severe or life-threatening thrombocytopenia in 73% patients		Rubin et al[24]
Lymphoma	TBI or HBI of 10–15 cGy/fraction, 2–3 fractions/week, 150 cGy total	Mild decrease in blood counts, none fell below normal ranges			Sakamoto et al[34]
Low grade localized follicular NHL	Two courses of 75 cGy separated by 2 weeks. Four weeks after TBI, involved areas treated with 40 Gy in 20 fractions	Granulocyte mean nadir of 3.9x10^3 cells/μL	Mean nadir of 124x10^3 cells/μL	Hemoglobin mean nadir of 13.4 g/dL	Richaud et al[35]
Oat cell carcinoma of the bronchus	TBI of 10 cGy/fractions, 5 fractions/week, 100 cGy total	No reported toxicity			Qasim et al[36]
HD-RT					

(continued)

Table 2. (continued)

Cancer type	Dose/fractionation regimen	Hematological toxicities			Reference
		Leukocytes	Thrombocytes	Erythrocytes/ hemoglobin	
Head and neck, chest, or pelvis	45–70 Gy	Leukocytes: Mean decrease of 14-15% Neutrophils: Mean decrease of 14-28% Lymphocytes: Mean decrease of 51-68%			Zacharia et al[40]
Gynecologic malignancy	45 Gy, whole pelvis	Grade 2 (CTCAE) leukopenia in 10.2% Grade 2 granulocytopenia in 1.9%		Grade 2 hemoglobin toxicity in 1.2%	Brixey et al[41]
Prostate or bladder	Prostate cancer: 76 Gy Bladder cancer: 60–70 Gy	Leukocyte counts reduced by 33.02% Neutrophil counts reduced by 23.78% Lymphocyte counts reduced by 62.19% and the only parameter with greater than grade 2 (CTCAE) toxicity. 19% of patients experienced grade 3 toxicity			Miszcyk and Majewski[42]
Testicular or ovarian	30–40 Gy in 13–14 fractions to the pelvis and paraaortic lymph nodes	Lymphocyte decline from $2.4x10^3$ cells/μL to $0.6x10^3$ cells/μL	Decreased 60% from initial mean of $315x10^3$ cells/μL to $195x10^3$ cells/μL		Campbell et al[43]
Advanced pancreatic cancer	59.4 Gy in 1.8 Gy fractions	Grade 1 (ECOG) hematologic toxicity in 37.7% Grade 2 in 11.3% Grade 3 in 9.4% of patients			Cohen et al[44]
High-risk early-stage cervical cancers	49.3 Gy in 29 fractions	Leukopenia in 58% Grade 4 granulocytopenia (SWOG) in 1 patient	Grade 1 (SWOG) thrombocytopenia in 8%	Grade 1 or 2 (SWOG) anemia in 22%	Peters et al[45]
Cervical cancer	50–50.4 Gy in 25–28 fractions of EBRT, followed by 30–36 Gy in 5–7 fractions of intracavitary brachytherapy	Grade 3 (CTCAE) or greater in 16.3%			Wang et al[46]
Breast cancer (stage 1-3)	60–65 Gy in 30–36 days	Leukocyte decrease from $4.81x10^3$ cells/μL to $3.4x10^3$ cell/μL 93% of patients experienced lymphopenia		Normal post treatment	Standish et al[47]
Early-stage breast cancer	56 Gy	Grade 1 (CTCAE) in 11 patients		Grade 1 (CTCAE) in 2 patients	Freedman et al[48]
Oat cell carcinoma of the bronchus	40 Gy in 20 fractions	Leukopenia (<3 $x10^3$ cells/μL) in 23%	Thrombocytopenia (<50 $x10^3$ cells/μL) in 23%		Qasim et al[36]
Chemotherapy					

(continued)

Table 2. (continued)

Cancer type	Dose/fractionation regimen	Hematological toxicities			Reference
		Leukocytes	Thrombocytes	Erythrocytes/ hemoglobin	
Advanced NHL	CVP (cyclophosphamide, vincristine, and prednisone) or C-MOPP	36% hospitalized due to leukopenia or infection	Thrombocytopenia in 30% with platelet counts $<50 \times 10^3$ cells/μL		Choi et al[33]
Advanced lymphoma	Single alkylating agent (cyclophosphamide or chlorambucil) or combination chemotherapy (CVP)	Leukopenia $<2 \times 10^3$ cells/μL in 11.8% of single agent and 17.6% of combination group	Severe thrombocytopenia $<50 \times 10^3$ cells/μL		Hoppe et al[25]
Low-grade NHL	CHVmP (cyclophosphamide, hydroxorubicin, adriamycin, VM-26)	Grade 3 (WHO) toxicity in 8%			Meerwaldt et al[23]
Advanced metastatic breast cancer	AC (adriamycin and cyclophosphamide), or ACMF (adriamycin, cyclophosphamide, methotrexate, and 5-fluorouracil)	8.3% hospitalized due to leukopenia Leukocytes $<3 \times 10^3$ cells/μL in 87.5% $<1 \times 10^3$ cells/μL in 31%			Kennealy et al[52]
Recurrent glioblastoma	PAC (procarbazine, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU, lomustine), and vincristine)	Grades 1-4 (WHO) leukopenia in 72.1%			Schmidt et al[53]
Taxane and hormone refractory prostate cancer	Ixabepilone or MP (mitoxantrone and prednisone)	Grade 3/4 (CTCAE) neutropenia in 54% of ixabepilone recipients and 63% of MP recipients 7 febrile neutropenia and one death due to neutropenic sepsis			Rosenberg et al[54]
Metastatic breast cancer	Paclitaxel and carboplatin	Grade 3/4 (CTCAE) neutropenia in 82%	Grade 3/4 (CTCAE) thrombocytopenia in 18%		Perez et al[55]
Resected bile duct cancer	Gemcitabine	Grade 4 (CTCAE) neutropenia in 13.3%			Ebata et al[56]
Follicular and mantle cell lymphoma	CHOP (cyclophosphamide, vincristine, doxorubicin, and prednisone) vs MCP (mitoxantrone, chlorambucil, and prednisone)	Grade 3/4 (WHO) leukopenia in 48% of CHOP Granulocytopenia in 42% MCP Grade 3/4 leukopenia in 67% Granulocytopenia in 58% 3% complication due to infection			Nickenig et al[57]
Advanced thymic carcinoma	CODE (cisplatin, vincristine, doxorubicin, and etoposide)	Some degree of leukopenia in all patients Neutropenia most common grade 4 toxicity (CTCAE)			Yoh et al[58]
Non-small cell lung cancer (NSCLC)	Pemetrexed or docetaxel	Grade 3/4 (CTCAE) neutropenia in 40.2% of pemetrexed Grade 3/4 neutropenia in 5.3% of docetaxel	Grade 3/4 (CTCAE) thrombocytopenia in less than 5%	Grade 3/4 (CTCAE) anemia in less than 5%	Hanna et al[59]

(continued)

Table 2. (continued)

Cancer type	Dose/fractionation regimen	Hematological toxicities			Reference
		Leukocytes	Thrombocytes	Erythrocytes/ hemoglobin	
Hormone refractory prostate cancer	Docetaxel	Grade 3/4 (CTCAE) leukopenia in 16% Grade 3/4 neutropenia in 16%	Grade 3/4 (CTCAE) anemia 4%		Beer et al[60]
NSCLC	Gemcitabine and cisplatin	Leukopenia in 85%	Thrombocytopenia in 96% Grade 3/4 (WHO) in 59.6%	All developed some grade of anemia	Van Zandwijk et al[61]
Locally advanced or metastatic pancreatic cancer	Gemcitabine and cisplatin	Leukopenia caused dose reduction in 17% and omission in 9%	Thrombocytopenia caused dose reduction in 65% and omission in 47%		Heinemann et al[62]
Chemoradiation					
Craniospinal irradiation (CSI)	Vincristine with 31.5–36 Gy in 18–20 fractions	Leukopenia in 100% with 15% developing infection	Thrombocytopenia in 70%	Anemia in 95% with 25% requiring blood transfusion due to grade 2 (CTCAE) anemia	Petersson et al[64]
Anaplastic thyroid carcinoma	Doxorubicin and cisplatin with 40 Gy	Grade 4 (WHO) neutropenia in 70%	Grade 3/4 (WHO) thrombocytopenia in 13%, and 1 patient needed platelet transfusions	Grade 3/4 anemia in 27% causing 6 patients to require transfusion with hemoglobin	De Crevoisier et al[65]
Gynecologic malignancies	Various chemotherapies with 45 Gy and 9 Gy boost in 1.8 Gy fractions	Leukopenia in 53.8% Neutropenia/ granulocytopenia in 15.4% Grade 4 (CTCAE) granulocytopenia and leukopenia occurred in 1 patient		Anemia in 92.3%	Salama et al[66]
Cervical cancer	Cisplatin with 45 Gy in 25 fractions. Boost dose of 50.4–59.4 Gy	Grade 1 (CTCAE) toxicities in 19.4%, grade 2 in 36.1%, and grade 3 in 27.8%			Beriwal et al[67]
Anal cancer	5-fluorouracil (5-FU) and mitomycin-c (MMC) with 45–59.4 Gy	Grade 1–4 neutropenia in 69.2% 1 hospitalization due to neutropenia and pulmonary embolism	Grade 1–4 thrombocytopenia in 46.2%	Grade 1–3 anemia in 76.9% Two patients needed RBC transfusions	Milano et al[68]
Anal cancer	5-fluorouracil (5-FU) and mitomycin-c (MMC) with 45–50.4 Gy	Addition of MMC to 5-FU increased hematologic toxicity from 3% to 18%			Flam et al[69]
Anal malignancies	Various chemotherapies with 54 Gy	Grade 1/2 leukopenia in 38%% Grade 3/4 leukopenia in 24%	Grade 1/2 thrombocytopenia in 27%% Grade 3/4 thrombocytopenia in 2%	Grade 1/2 anemia in 73%% Grade 3/4 leukopenia in 4%	Pepek et al[70]
High-grade astrocytoma	Cisplatin and BCNU with 50–60 Gy in 17 fractions	Leukopenia in 40–77% Leukopenia <1.0 x10^3 cells/ μL in 8–38%	Thrombocytopenia in 68–89%	Anemia was frequent and commonly required transfusions	Kleinberg et al[71]

(continued)

Table 2. (continued)

Cancer type	Dose/fractionation regimen	Hematological toxicities			Reference
		Leukocytes	Thrombocytes	Erythrocytes/ hemoglobin	
Bladder cancer	Gemcitabine or cisplatin with 50 Gy in 20 fractions	Grade 1-4 (CTCAE) toxicity in 87.5%			Turgeon et al[72]
Cervical cancer	Cisplatin with 50–50.4 Gy EBRT in 25–28 fractions, followed by 30–36 Gy intracavitary brachytherapy in 5–7 fractions	Grade 3/4 hematologic toxicity (CTCAE) in 62.5%			Wang et al[46]
Pancreatic cancer	5-fluorouracil and mitomycin-c with 59.4 Gy in 1.8 Gy fractions	Grade 1–4 hematologic toxicity in 85.5%			Cohen et al[44]
Gynecologic malignancies	Various chemotherapies with 45 Gy	Grade 2 or greater leukopenia in 47.2% Neutropenia in 16.6%		Anemia in 19.4%	Brixey et al[41]

Three percent of patients experienced grade 1 (WHO) toxicity, 6% had grade 2 toxicity, and one patient had extensive involvement of the bone marrow causing them to experience grade 3 thrombocytopenia. Overall, hematologic toxicity had an average increase in grade of 2.1 for thrombocytes and 2.2 for leukocytes. Similarly, Safwat et al[32] treated a group of 35 relapsed and/or chemo-resistant patients with NHL using 2 cycles of TBI in 4 20 cGy fractions, to a total dose of 160 cGy. Hemoglobin $^{<}$10 g/dL causing anemia developed in 20% of patients, and leukopenia of $^{<}3.9x10^3/\mu L$ developed in 45.7% of patients, of which one patient had continued neutropenia requiring transfusion with growth factor. Thrombocytopenia $^{<}100x10^3/\mu L$ occurred in 54.3% of patients, 73.7% of whom had platelet counts continue to decrease below $50x10^3/\mu L$ resulting in 71.4% requiring at least one platelet transfusion over the study period. Overall, TBI was deemed effective for the palliation of relapsed and chemo-resistant patients with NHL.

Many clinical trials compared LD-RT with standard of care chemotherapy. In those studies, toxicities in patients who received LD-RT, similar to those who received chemotherapy, included leukopenia and thrombocytopenia. Even though reports were similar, they were overall milder in the group of patients who received LD-RT compared to chemotherapy. Choi et al.[33] studied 39 patients with advanced NHL treated with fractionated TBI to a total of 150 cGy. Thrombocytopenia frequently caused treatment interruptions in this cohort and was the major toxicity in the trial with a median nadir platelet count of $77x10^3/\mu L$, although no major hemorrhage was reported in these patients. In addition to platelet changes, the median nadir WBC count was $3.7x10^3/\mu L$; however, despite this reported reduction in WBC counts, no infections occurred. In comparison, this same study offered 50 patients who were treated with combination chemotherapy, of which 30% developed thrombocytopenia with platelet counts $<50\ x10^3/\mu L$. In addition, 36% of chemotherapy patients were hospitalized due to leukopenia or infection, which was a more severe issue than treatment with TBI. Hoppe et al.[25] conducted a study of advanced lymphoma patients randomized into 3 different treatment groups; single agent (SA) chemotherapy, combination chemotherapy (CVP), or TBI. TBI was delivered to a total of 150 cGy in 2–3 fractions/week. Patients in the CVP group had the highest incidence of hospitalization for infection or fever with 7 events in 5 patients. Severe leukopenia ($<2x10^3/\mu L$) occurred equally among the 3 groups: 11.8% in SA, 17.6% in CVP, and 17.6% in TBI. Severe thrombocytopenia ($<50x10^3/\mu L$) occurred in 17.6% of 17 patients receiving TBI.

A European Organization for Research and Treatment of Cancer (EORTC) Lymphoma Cooperative Group study reviewed by Meerwaldt et al.[23] examined 84 patients who received either TBI or aggressive combination chemotherapy for the treatment of low-grade NHL. TBI was given 3 fractions/week of 10 cGy, to a total dose of 250 cGy. Following treatment, 44% of patients developed grade 3 (WHO) toxicity and 16% grade 4. One patient died from hematologic toxicity; however, this was due to an error in treatment administration where a boost dose was started too soon after the completion of TBI and bone marrow was not able to recover. Eight percent of patients in the chemotherapy group developed grade 3 hematologic toxicity.

Some of the most severe hematological effects were reported by Rubin *et al.*[24]who evaluated 56 patients with advanced lymphocytic lymphoma, where 26 received one of 2 TBI regimes. Initially, TBI patients received 150 cGy in 10 cGy fractions over a 5-week period. Severe or life-threatening granulocytopenia or thrombocytopenia occurred

in 73% patients. Eight of these cases were life threatening and one patient died as a result of an infection. After this outcome occurred, the scheduling system of TBI doses was then changed to ensure that patients received an overall lower total dose of 50 cGy in 5 cGy fractions over 2 weeks. Hematological effects were reduced in this group, with 43% experiencing severe or life-threatening leukopenia, or thrombocytopenia. Three life-threatening cases were due to a combination of both thrombocytopenia and leukopenia. After cessation of treatment the hematologic toxicity reversed quickly within 1–2 weeks.

Not all LD-RT clinical trials have observed major hematological effects. Three studies found no major changes in leukocytes or thrombocytes following TBI. Sakamoto[34] presented the result of an early clinical trial using TBI alone or in conjunction with localized fields. The LD-RT portion of the treatment consisted of either TBI or half-body irradiation (HBI) 2–3 times per week in 10–15 cGy fractions for a total of 150 cGy. Although a mild decrease in blood counts was reported, none fell below normal ranges. Richaud et al[35] examined LD-RT for low grade localized follicular NHL between 1986 and 1994. Treatment consisted of 2 courses of 75 cGy which were separated by a period of 2 weeks for rest. Four weeks after the second course of TBI the involved areas were treated to 40 Gy in 20 fractions. Clinical tolerance was excellent, and no treatments delays were needed. The mean nadir values for blood counts were 3.9 $x10^3/\mu L$ for granulocytes, 13.4 g/dL for hemoglobin, and $124x10^3/\mu L$ for thrombocytes. One of the only studies to investigate LD-RT on non-hematological malignancies was Qasim,[36] who treated 30 patients diagnosed with oat cell carcinoma of the bronchus. TBI was delivered in 10 cGy/fractions 5 fractions/week to a total dose of 100 cGy. There was no reported toxicity as a result of the TBI portion of treatment in the first 2 weeks of the study. TBI was followed by HD-RT beginning immediately after the third week of treatment, of which the resulting hematologic changes will be discussed in the HD-RT section.

Overall, all reported treatments with LD-RT were said to be well or very well tolerated. The majority of these studies reported their most common hematologic toxicities to be thrombocytopenia and to a lesser degree leukopenia. However, even when it was necessary to reduce or omit doses, most reported only mild (grade 1–2) toxicities which returned to normal levels shortly after treatment was concluded. Additionally, some studies found no significant changes in blood counts due to treatment with TBI or mild depression that did not fall below the normal range. A number of these studies compared LD-RT to chemotherapy and found a lower incidence of morbidity with similar survival in the groups receiving low dose radiation treatments.[25,33]

High Dose Radiation Therapy. High dose radiation therapy has been used in the management of cancer for over 100 years and over this time has maintained its status as an integral part of cancer treatment.[37] Conventional HD-RT relies on high doses of radiation (most commonly high energy x-rays) in efforts to damage the DNA of cancer cells, where repeated fractionated exposures result in cell death and inability to reproduce.[37] Prior to the discovery of x-rays in 1895 options for the treatment of benign or malignant growths were very limited, and when the first cancer patients were treated with x-rays little was understood about the biological effects of radiation.[37] However, since 1960, many technological advances have been made in order to decrease side effects while providing maximum tumor dose.[38] The introduction of 3D conformal radiation therapy (3D-CRT), which uses computed tomography (CT) to plan out and optimize each patient's individual treatment plan, has allowed for safer and more effective treatments.[37] The new designation of radiation oncology has introduced the most effective and precise methods of radiation therapy treatment including intensity modulated radiation therapy (IMRT), stereotactic radiosurgery, and additional advancements such as combined chemoradiation therapy treatment.[38]

Today, roughly 2 thirds of all cancer patients are treated with radiation therapy. However, one of the commonly reported side effects of radiation therapy includes hematological changes caused by suppression of the bone marrow leading to fewer blood cells being made and blood counts decreasing below normal values.[37,39] For this reason, acute bone marrow suppression is a major dose limiting side effect of conventionally dosed radiation therapy treatments that requires careful consideration.[39,40] A study by Zachariah et al.[40] assessed blood counts in 299 cancer patients receiving conventional fractionated radiation therapy to the head and neck, chest, or pelvis. Patients were treated with doses of 45–70 Gy. Across all tumor sites, leukocyte counts saw a mean decrease of 14–15% from baseline to end of treatment, with neutrophil counts decreased by 14–28% and lymphocyte counts decreased by 51–68%. These CBC changes were found to be statistically significant, although the results were not considered clinically significant.

Roughly 40% of all bone marrow in adults is contained within the bones of the pelvis, making hematologic toxicity a major risk in patients receiving pelvic radiation therapy.[41] Brixey et al.[41] reviewed hematologic toxicity in patients being treated for gynecologic malignancies with a dose of 45 Gy to the whole pelvis. Leukopenia was the most common clinically significant effect, with grade 2 (CTCAE) toxicity occurring in 10.2% of patients. Grade 2 granulocyte and hemoglobin toxicity also occurred in 1.9% and 1.2% of patients, respectively. Similarly, Miszcyk and Majewski[42] described the treatment of 115 patients with prostate or bladder cancer through definitive radical radiation therapy. All 74 prostate cancer patients received 76 Gy to the primary tumor while the patients with bladder cancer received a range of total doses between 60–70 Gy. Leukocyte counts were reduced by 33.02% over the course of the treatment, with neutrophils decreasing by 23.78%. Lymphocyte counts had the greatest

reduction with a mean decrease of 62.19% and was the only hematological parameter with greater than grade 2 (CTCAE) toxicity where 19% of patients experienced grade 3 toxicity. Campbell et al.[43] followed 10 patients receiving HD-RT for testicular or ovarian malignancies. The pelvis and paraaortic lymph nodes received between 30–40 Gy in 13–14 fractions over the course of roughly 1 month. Lymphocytes were impacted the most, declining from $2.4x10^3/\mu L$ at the beginning of treatment to $0.6x10^3/\mu L$. After 12 months lymphocyte counts were still significantly lower than pre-treatment at less than 60% of starting values and a mean of $1.4x10^3/\mu L$. Platelet counts also dropped by approximately 60% from an initial mean of $315x10^3/\mu L$ to $195x10^3/\mu L$. After 12 months platelet counts remained significantly lower than pre-treatment values at $227x10^3/\mu L$.

Cohen et al[44] observed 108 patients diagnosed with locally advanced pancreatic cancer and received either radiation therapy alone or chemoradiation. All patients received a total radiation dose of 59.4 Gy in 1.8 Gy fractions. Hematologic toxicities were the most commonly reported side effect in both treatment groups; however, the degree of toxicity was more severe in patients receiving chemoradiation. In the 53 patients treated exclusively with radiation therapy, grade 1 (ECOG) hematologic toxicity occurred in 37.7% of patients, grade 2 in 11.3% of patients, and grade 3 in 9.4% of patients. In a similar comparative study between radiation therapy and combination chemoradiation, high-risk early-stage cervical cancers were treated with 49.3 Gy in 29 fractions.[45] From the 112 patients receiving only radiation therapy, leukopenia was the most common hematologic toxicity in 58% of patients. Twenty two percent of patients developed grade 1 or grade 2 anemia and only 8% had mild, grade 1 thrombocytopenia. Granulocytopenia and infection were the only parameters to reach a grade 4 toxicity (SWOG scale) in 1 patient each. Again, hematologic toxicity was significantly more common in the concurrent chemoradiation group compared to HD-RT alone. Finally, Wang et al[46] analyzed patients with cervical cancer who received radical radiation therapy alone or with concurrent chemotherapy. Forty-nine patients were treated with EBRT of 50–50.4 Gy in 25–28 fractions, followed by 30–36 Gy in 5–7 fractions of intracavitary brachytherapy. Among these patients, 16.3% experienced grade 3 (CTCAE) or greater hematologic toxicity.

In patients where the radiation field did not include the pelvis, more minimal hematological toxicities were often reported. Standish et al.[47] analyzed 14 patients with stage 1–3 breast cancer who received radiation therapy treatments, following previous treatments of chemotherapy, to a total dose of 60–65 Gy over 30–36 days. In the majority of patients, leukocyte counts had recovered to normal levels after chemotherapy, prior to beginning radiation therapy. At the end of radiation therapy, mean leukocyte count had decreased significantly, from a mean of $4.81x10^3/\mu L$ to $3.4x10^3/\mu L$. Lymphocytes were the most affected with 93% of patients experiencing lymphopenia and the mean decreasing by 39%. Neutrophil counts were mildly decreased after treatment, and erythrocytes and hemoglobin counts were normal post-treatment. Similarly, Freedman et al[48] found minimal hematologic toxicity in 75 patients treated with HD-RT for early-stage breast cancer. The field consisted of the whole breast plus a boost to a smaller volume for a total dose of 56 Gy. Hematologic toxicity was limited to grade 1 (CTCAE) which presented in 11 patients with anemia and 2 with neutropenia.

In a study by Qasim[36] (discussed in the preceding section), HD-RT was given immediately following the LD-RT treatments for carcinoma of the bronchus. From the third week of treatment, 40 Gy was given in 20 fractions to the tumor, whole mediastinum, and both supraclavicular fossae. In the last 2 weeks 20 Gy in 10 fractions was given with the field extended to include the liver. Thrombocytopenia and leukopenia were the most common toxicities throughout the study due to the HD-RT, experienced mildly by most participants. More severe thrombocytopenia ($<50x10^3/\mu L$) and leukopenia ($<3x10^3/\mu L$) occurred in 23% of patients. It is worth noting that since this treatment was administered immediately after LD-RT, it cannot be confidently said whether or not these effects occurred only due to the HD-RT.

Overall, due to HD-RT being prescribed as a targeted therapy, the severity of hematological effects is dependent on the location and the tissues involved in the treatment field. As one could expect, most severe toxicities were reported from studies when the field would include the pelvis, an area with a large amount of bone marrow. With HD-RT the most common hematological effect reported in patients was leukopenia, more specifically lymphocyte counts were the most severely impacted. Anemia and thrombocytopenia were also reported in studies involving HD-RT for cancer treatment, although this was less common and milder in nature.

Chemotherapy. Chemotherapy is a treatment that is generally delivered systemically and uses cytotoxic agents to damage the DNA of rapidly proliferating cells, such as cancer cells.[49] In the 1940's, examination of the blood of military workers who were exposed to mustard gas in World War 2 prompted the journey into chemotherapy research.[50] Blood from these men was found to have significantly reduced leukocyte counts with notably depleted bone marrow and lymph nodes.[50] This discovery sparked investigation into the chemistry of mustard compounds and its potential therapeutic effects.[50] Early studies of nitrogen mustard showed tumor regression in mice with transplanted lymphoid tumors which obtained great support and prompted studies to begin on humans. When nitrogen mustard was given to patients with lymphoma there was significant regression of their disease.[50] By the end of the 1960s it was determined that cytotoxic drugs could cure cancer, and through the evolution of chemotherapy there are currently over 100 different cytotoxic agents in clinical use.[50] Chemotherapy works by targeting cells that are in the process of cell division, making malignancy one of its main targets. Unfortunately, since this process is not specific it will also affect any normal cells that multiply at rapid rates. The tissues

most commonly affected by chemotherapy are often highlighted by the common side effects such as changes in hair growth, skin, digestive issues (as the lining of the digestive tract are affected) in addition to reproductive cells, and bone marrow. Clinically it is important to monitor a patient's hematological changes as chemotherapy can prevent bone marrow from being able to adequately replenish the blood cells, resulting in low blood counts and risk of complications.[51]

A commonly reported hematological toxicity caused by chemotherapy is a reduction in leukocyte counts. Kennealy et al[52] reported on 48 women with advanced metastatic breast cancer. These women received one of 2 chemotherapy regimens of either adriamycin and cyclophosphamide (AC), or adriamycin, cyclophosphamide, methotrexate, and 5-fluorouracil (ACMF). Leukopenia was common and caused 8.3% of patients to be hospitalized. Leukocyte counts of $<3x10^3/\mu L$ occurred in 87.5% of patients, 31% of which had $<1x10^3/\mu L$. Similarly, Schmidt et al[53] used a PAC (procarbazine, 1-(2-chloroethyl)-3- cyclohexyl-1-nitrosourea (CCNU, lomustine), and vincristine) regimen for the treatment of recurrent glioblastoma and observed leukopenia of grades 1-4 (WHO) in 72.1% of patients. Treatment was discontinued in 14.6% of patients due to hematologic toxicity.

Neutrophils appear to be the main leukocyte that is impacted by chemotherapy. Rosenberg et al[54] randomized 86 patients to receive either ixabepilone or mitoxantrone and prednisone (MP) as a second line chemotherapy treatment for their taxane and hormone refractory prostate cancer. The most common grade 3/4 (CTCAE) toxicity was neutropenia, occurring in 54% of ixabepilone recipients and 63% of MP recipients. Of these patients, 7 developed febrile neutropenia and one died due to neutropenic sepsis. Similarly, Perez et al[55] evaluated the toxicity of first line chemotherapy using paclitaxel and carboplatin to treat metastatic breast cancer in 50 patients. The most common grade 3/4 (CTCAE) toxicity was neutropenia, occurring in 82% of patients. Grade 3/4 thrombocytopenia also occurred, but only in 18% of patients. Ebata et al[56] assigned 113 patients with resected bile duct cancer to receive either adjuvant gemcitabine or observation after surgery. Grade 3 or greater toxicity (CTCAE) was common, the most frequent of these was neutropenia. In addition, 13.3% of patients developed grade 4 neutropenia.

Nickenig et al[57] recorded the use of CHOP (cyclophosphamide, vincristine, doxorubicin, and prednisone) chemotherapy vs MCP (mitoxantrone, chlorambucil, and prednisone) to treat patients with follicular and mantle cell lymphomas. Leukopenia and granulocytopenia had the highest incidence of toxicity. Grade 3/4 leukopenia (WHO) occurred in 48% in the CHOP group vs 67% in the MCP group, while granulocytopenia occurred in 42% in the CHOP arm vs 58% in the MCP arm. Both arms had 3% of patients experience complications due to infection. Weekly cisplatin, vincristine, doxorubicin, and etoposide (CODE) administration was used by Yoh et al[58] to treat advanced thymic carcinoma in 12 patients. Neutropenia was the most common grade 4 toxicity (CTCAE), however, leukopenia of some grade occurred in all patients.

One of the largest studies was performed by Hanna et al,[59] who assessed 541 patients with non-small cell lung cancer (NSCLC). Patients were randomized to receive either pemetrexed or docetaxel. There was a total of 8 deaths due to treatment, 5 from docetaxel, and 3 for pemetrexed. Patients receiving docetaxel experienced more severe hematological toxicities, with 40.2% developing grade 3/4 neutropenia (CTCAE), compared to only 5.3% in the pemetrexed group. Anemia and thrombocytopenia were lower, with grade 3/4 toxicities occurring in less than 5% of patients. Docetaxel toxicities were also identified by Beer et al,[60] who studied 25 patients with hormone refractory prostate cancer. Grade 3/4 (CTCAE) leukopenia, neutropenia, and anemia, occurred in 16%, 16%, and 4% of patients, respectively.

In addition to leukopenia, several studies have documented a significant decrease in thrombocytes and erythrocytes. A study by the EORTC Lung Cooperative Group followed 47 chemo-naïve patients with NSCLC treated with gemcitabine and cisplatin.[61] Throughout 127 cycles of chemotherapy, all patients developed some grade of anemia. Thrombocytopenia occurred in 96% of patients, 59.6% of which were classified as grade 3/4 (WHO). Leukopenia was also present in 85% of patients. In total, 34% of omissions and 23% of reductions in gemcitabine treatment were due to low blood counts. Heinemann et al.[62] evaluated 35 chemo-naïve patients with locally advanced or metastatic pancreatic cancer who received gemcitabine and cisplatin identified thrombocytopenia as the major toxicity. Thrombocytopenia caused dose reduction and omission in 65% and 47% of cases, respectively, and resulted in grade 4 toxicities (WHO). Grade 4 neutropenia was also observed, while leukopenia caused dose reduction in 17% and omission in 9%, but without grade 4 toxicity.

Overall, across the variety of chemotherapeutics used in these studies, high grade (3/4) hematologic toxicity was widespread for leukocytes, mainly neutropenia. Fever and infection were common in these patients often leading to hospitalization, and in some cases even death.[52,54,63] It was less common for thrombocytopenia or anemia to present as the main hematologic toxicity; however, this was the case in several studies although no adverse bleeding events occurred.[53,61,62]

Chemoradiation Therapy. Several studies have examined hematological toxicities in patients receiving a combination of chemotherapy and HD-RT. Petersson et al.[64] initiated a study after observing unexpectedly severe hematologic toxicity in 2 patients receiving craniospinal irradiation (CSI). In their study, twenty adult men received CSI with doses ranging from 31.5 to 36 Gy in 18–20 fractions, and 13 patients received concurrent chemotherapy. Leukopenia, thrombocytopenia, and anemia occurred in 100%, 95%, and 70% of all patients, respectively. Twenty-five percent of patients required blood transfusions due to grade 2 (CTCAE) anemia, while 15% of patients developed infection causing one patient to discontinue treatment entirely.

A combined treatment protocol for anaplastic thyroid carcinoma in 30 patients was analyzed by De Crevoisier et al[65] consisting of surgery, chemotherapy with doxorubicin and cisplatin, and radiation therapy of 40 Gy. Neutropenia was the most common hematologic toxicity where 70% of patients endured grade 4 (WHO) toxicity. Grade 3/4 anemia occurred in 27% of patients causing 6 patients to require transfusion with hemoglobin. One patient required platelet transfusion due to thrombocytopenia which was observed as grade 3/4 toxicity in 13%. Additionally, chemotherapy doses were reduced by 30% in 5 patients due to hematologic toxicity.

Chemoradiation is a common treatment for gynecological cancers. A study by Salama et al.[66] took place from 2002 to 2005 using extended field intensity modulated radiation therapy (EF-IMRT) to treat 13 patients with various gynecologic malignancies. All but one patient received concurrent chemotherapy. The treatment field included the pelvis along with the paraaortic, and presacral lymph nodes and was given a total of 45 Gy with a 9 Gy boost to patients with gross disease, both delivered in 1.8 Gy fractions. The most common hematologic toxicity was anemia which was experienced by 92.3% of patients. Otherwise, 53.8% of patients developed leukopenia and 15.4% developed neutropenia/granulocytopenia. Grade 4 (CTCAE) granulocytopenia and leukopenia each occurred in 7.7% (one patient). Similarly, Beriwal et al[67] reported 36 patients treated with extended field intensity modulated radiation therapy and concurrent cisplatin chemotherapy for the treatment of cervical cancer. Radiation doses of 45 Gy were delivered in 25 fractions (with a boost dose of 50.4–59.4 Gy in some patients) while the nodes received 55–60. Additionally, all but 2 patients received brachytherapy. Grade 1 (CTCAE) bone marrow toxicities were observed in 19.4% of patients, grade 2 in 36.1%, and grade 3 in 27.8%. Grade 3 hematologic toxicity occurred exclusively due to leukopenia in all 27.8% of patients. 13.9% required a pause in their treatment course and 8.3% had their final dose of chemotherapy omitted.

Chemoradiation is also commonly used in the treatment of anal cancers. Milano et al[68] assessed 13 patients with squamous cell carcinoma of the anus treated using intensity modulated radiation therapy of 45–59.4 Gy and concurrent chemotherapy with 5-fluorouracil (5-FU) and mitomycin-c (MMC). All patients developed leukopenia. Absolute neutrophil counts and thrombocytopenia of grade 1–4 were experienced by 69.2% and 46.2% of patients, respectively. Additionally, grade 1–3 anemia was present in 76.9% of patients. One patient had their final fraction of radiation omitted because of decreased blood counts and dehydration, another was hospitalized for 2 weeks due to neutropenia and pulmonary embolism, and 2 patients required red blood cell transfusions. Increased hematologic toxicity resulting from the addition of MCC was also reported by Flam et al[69] who used concurrent chemoradiation to treat anal cancer. The addition of MMC to 5-FU increased hematologic toxicity from 3% to 18% and resulted in significantly more neutropenia and thrombocytopenia. Although there were no significant complications due to bleeding, infection was linked to the increase in neutropenia. Additionally, fatal toxicity occurred in only 1 patient in the 5-FU arm vs 4 patients in the combination arm and all were due to neutropenic sepsis. Finally, Pepek et al[70] reviewed patients receiving concurrent chemoradiation therapy where the average radiation therapy dose was 54 Gy. Grade 3/4 (CTCAE) hematological toxicity was experienced by 24% of patients. Leukopenia was the most common grade 3/4 toxicity which occurred in 24%, while 38% experienced grade 1/2 leukopenia. Grade 1/2 thrombocytopenia was present in 27% of patients, but only 2% (1 patient) had grade 3/4 platelet toxicity. Anemia was the most common grade 1/2 toxicity and occurred in 73%; however, only 4% experienced grade 3/4 toxicity. The presence of leukopenia and thrombocytopenia caused 1 patient who was receiving 5-FU and MMC to pause treatment.

Chemotherapy that is delivered concurrently during radiation therapy, as opposed to following radiation therapy, produces more severe hematological toxicities as shown by Kleinberg et al[71] who reviewed the effects of a chemotherapy regimen of cisplatin and carmustine (BCNU) coupled with radiation therapy. One arm of the treatment received radiation therapy after the 3 cycles of chemotherapy were complete (sequential) and the other arm received radiation therapy during the first 2 cycles (concurrent). Radiation doses of 50–60 Gy were delivered in 17 fractions. Leukopenia and thrombocytopenia were both increased in the concurrent chemoradiation therapy arm. Overall occurrence of leukopenia was 40% in the sequential group and 77% in the concurrent group. Additionally, 8% of sequential patients experienced leukopenia $<1.0\ x10^3/\mu L$ as opposed to 38% who were treated concurrently. Thrombocytopenia incidence rose from 68% to 89% in patients receiving concurrent treatment. Incidence of anemia was not dependent on treatment type but was frequent and commonly required transfusions.

Turgeon et al[72] treated 24 patients over the age of 70 with radical concurrent chemoradiation for invasive bladder cancer. Radiation therapy was prescribed as 50 Gy in 20 fractions and all patients received concurrent chemotherapy in the form of either gemcitabine or cisplatin. Grade 1–4 (CTCAE) hematologic toxicity occurred in 87.5% of patients, where 4.2% (one patient) were hospitalized for febrile neutropenia.

Several of the studies previously discussed in the HD-RT and chemotherapy sections also included concurrent treatments. Wang et al[46] treated 24 patients with chemoradiation for cervical cancer. Grade 3/4 hematologic toxicity (CTCAE) occurred in 62.5% of patients. Cohen et al[44] treated 55 patients received concurrent chemotherapy in the form of 5-fluorouracil and mitomycin-c in addition to radiation therapy. Grade 1–4 hematologic toxicity occurred in 85.5% of patients. In the review by Brixey et al[41] leukopenia was the most common grade 2 or higher toxicity which occurred in 47.2% of patients. Additionally, ANC toxicity occurred in 16.6% of these patients, and hemoglobin toxicity in 19.4%. In general, there was an increased incidence of hematologic toxicity in these cohorts compared to their counterparts receiving single modality treatment.

For combination chemoradiation therapy regimens, leukopenia and neutropenia were the overall most common

hematologic toxicities as well as the most common high grade (grade 3/4) toxicities. Various cases of hospitalization, infection, fevers, and deaths due to neutropenia occurred. Hematologic toxicity was widespread as thrombocytopenia and anemia were also prevalent among these groups, as well as the occurrence of erythrocytopenia. Several blood transfusions were needed including platelet, and RBC transfusions.

Discussion

This review summarizes hematological changes that occur as a result of current standard of care cancer treatments, with specific focus on introducing LD-RT as a treatment option. Low dose radiation has shown promise in altering immune function and potential as a cancer therapeutic.[17] One of the benefits LD-RT can offer over other options is its minimal adverse side effects, which often negatively impact a patient's quality of life. Previous clinical trials using LD-RT have documented hematological changes during treatment, which has often been used as an argument as to why LD-RT should not be brought into modern treatment. However, current standard of care options for cancer patients also include similar hematological changes. To date, hematological toxicities from cancer treatment have not been adequately assessed to determine if LD-RT should be disregarded for this principle alone. This review compares clinically evaluated hematological changes following conventional cancer therapies (HD-RT, chemotherapy, and chemoradiation) in addition to hematological changes observed with LD-RT. Patients being treated with LD-RT had fewer hematological toxicities compared to other treatment modalities. Although there were a few severe hematologic toxicities reported, they were often lower grade than those experienced in the other therapies (Table 3).[33] In several studies, blood counts did not fall below normal ranges.[34] Low dose radiation treatments were well tolerated and described as superior in terms of simplicity and decreased morbidity.[33] There was also a lower rate of complications and death when compared to other treatments, in particular chemotherapy.[25,33]

LD-RT is a safe and effective treatment option with multiple different applications in cancer management. When comparing LD-RT to chemotherapy, the 2 do not produce statistically significant differences in complete and partial response, overall survival, or relapse free survival rates or duration. For example, Meerwaldt et al[23] showed a 36% complete remission rate for TBI vs 55% for combination chemotherapy, and overall response rates were 76% vs 69%, respectively. Survival for both groups was 75% at 3 years and progression free survival was similar with 78% failure in the TBI group and 77% failure in those who received combination chemotherapy. Partial response between the TBI and chemotherapy groups in the study by Rubin et al[24] were 58% and 54%, respectively. What differed significantly in this study was the median duration of response which was 18 weeks for TBI and 48 weeks for chemotherapy. However, median length of survival was still nearly identical at 136 weeks in the TBI group vs 135 weeks for the chemotherapy group. LD-RT has also been associated with a potential ability to prevent or delay the development of distant metastasis.[36] In addition to its use as a primary treatment option, LD-RT is an excellent primer for other therapies such as chemotherapy or boost doses of HD-RT. TBI may also be a better option for palliative treatment than chemotherapy and is effective in patients who have relapsed following prior chemotherapy.[32]

Hematological toxicities associated with HD-RT differed from those observed in LD-RT, whereas LD-RT primarily impacted thrombocytes, HD-RT largely affected WBCs, in particular lymphocytes. Since HD-RT is not a systemic treatment, the severity of effects largely depended on the type of cancer being treated and the organs included in the radiation field. Most of the severe hematological effects occurred in patients with gynecological cancers, which is not surprising given that 40% of the body's bone marrow lies in the pelvic bones.[41] In addition to the effects on bone marrow stem cells, HD-RT can directly impact lymphocytes, which are known to be more radiosensitive compared to other blood cell types. Therefore, radiation fields that include the lymph nodes can result in higher toxicities. Alternatively, in HD-RT with treatment fields that did not include the pelvis, such as breast cancer, patients did not develop high grades of hematologic toxicity and many blood counts remained in the normal rages.[47,48] This is the results of smaller volumes of bone marrow and lymph nodes in these areas.

In the cohort of chemotherapy treatments, blood counts were widely affected leading to patients experiencing thrombocytopenia, leukopenia, neutropenia, and anemia. Chemotherapy is a systemic drug and targets all rapidly dividing cells such as the bone marrow. As blood cells are continually produced within the bone marrow, the effects of chemotherapy lead to the widespread depression of blood counts. Similar to HD-RT, the most common toxicity was leukopenia. However, whereas HD-RT predominantly impacted lymphocytes, chemotherapy has a greater impact on granulocytes. There was also a high prevalence of fever and infection due to treatment, resulting in hospitalizations for patients. Given the low levels of leukocytes, including

Table 3. Summary of Hematological Changes Resulting from Various Cancer Therapies. Arrows Indicate the Average Grade of Blood Cell Type Depression.

	Leukocytes	Thrombocytes	Erythrocytes/ hemoglobin
Low dose radiation therapy	↓	↓↓	–
High dose radiation therapy	↓↓	↓	↓
Chemotherapy	↓↓↓	↓↓	↓
Chemoradiation therapy	↓↓↓	↓↓	↓↓

neutrophils, and their role in immunity, leukopenia and neutropenia impair the ability of the body to fight off infections. In the reviewed studies, deaths that were observed in patients were due to infection and sepsis result from the immunocompromised status of the patients, and their inability to adequately clear infection from their bodies.

In general, the addition of a concurrent treatment to a single method leads to increased incidence of hematologic toxicity. This was particularly evident in patients receiving combination chemoradiation therapy regimens. The systemic effects of chemotherapy drugs coupled with the effects of HD-RT on the bone marrow in the field, ultimately leads to increased strain on the hematopoietic system and its production of blood cells. In all the studies that compared single modality to combination treatments, there was an increase in hematologic toxicity in those receiving combination chemoradiation therapy. Consistent with both the chemotherapy and HD-RT results, hematologic toxicity in patients receiving combination chemoradiation therapy was overall more common and more severe for leukopenia. Considering the separate effects that each of these treatments has on the number of immune cells circulating through the body, combining them produces the same adverse events but more amplified than when treatments are independent of one another. In addition to leukopenia, these combined treatments also produced widespread effects on platelets, and erythrocytes.

In addition to hematological toxicities, cancer therapeutics can lead to numerous other side effects. With LD-RT though, the non-hematologic toxicities consisted only of mild fatigue, slight weakness, minor loss of appetite,[33,35] and one patient in the study by Meerwaldt et al[23] had grade 3 (WHO) gastrointestinal toxicity. In contrast, HD-RT often causes more notable side effects within the treatment field. General side effects that occur commonly from HD-RT treatments include fatigue, skin reactions such as erythema, dry and moist desquamation, and pruritus, change in skin pigmentation.[11] Other site-specific side effects can occur depending on the organs and tissues irradiated. Hair loss and increased intracranial pressure can occur from cranial radiation.[11] Xerostomia, mucositis, and oral cavity infections such as thrush, dysgeusia, dysphagia, and odynophagia can occur due to treatment of head and neck cancers.[11] When irradiating the chest, patients generally experience dyspnea and at times lymphedema or brachial plexopathy can be caused or exacerbated by treatment.[11] Nausea and vomiting is the most common side effect particular to abdominal irradiation.[11] When treating the pelvis, the most common side effects are cystitis, and diarrhea due to enteritis or proctitis which is also marked by tenesmus, pain, rectal bleeding, and telangiectasis.[11,73] Following chemotherapy, nausea and vomiting, and alopecia are nearly universal. Other frequent side effects include bone marrow suppression, neuropathy, mucositis, and gastrointestinal toxicity.[73] Unfortunately, the intervention for these side effects often includes dose reduction of the chemotherapy drugs which is linked to reduced survival.[74]

Hesitancy around the use of radiation is no new phenomenon. Secondary malignancy may be thought of as a concern when discussing treatments with LD-RT as the field size targets large volumes of tissue. Overall, radiation induced secondary malignancies are generally less of a concern in older adults due to their shorter life expectancy coupled with the potentially long latency period for development of the malignancy. However, there is a higher concern in pediatric cancer cases. Unfortunately, no studies reviewed in the LD-RT section of this paper followed patients long-term to assess the development of secondary malignancy. The most analogous population to assess potential risks is patients receiving high dose total body irradiation as a conditioning treatment for hematopoietic stem cell transplant. However, doses in these therapies are considerably higher compared to what is employed in LD-RT. Secondary malignancies have been identified in patients receiving TBI, but these risks become minimal as the radiation dose is reduced. For example, Baker et al[75] found an increased secondary malignancy risk following TBI doses of 600–1000 cGy. In contrast, patients who received TBI doses of 200–450 cGy did not have a significantly different risk of secondary malignancies compared to patients receiving chemotherapy. A dose of 200–450 cGy is still much higher than the typical doses used in LD-RT.

Much of the concern regarding potential carcinogenic effects of low dose radiation stems from the linear no-threshold (LNT) model. The LNT model suggests that adverse effects due to ionizing radiation exposure are directly proportional to dose, including in the low dose region. The LNT model was originally designed as a simplified model for use in radiation protection; however, it has become common practice to erroneously use the LNT model to assess cancer risk from medical or environmental exposures.[76] In fact, advances in radiation biology research have shown that the LNT model may not be accurate at low doses where biological processes do not respond the same way as they do at high doses.[17] Instead low dose radiation has been shown to activate many cellular defense mechanisms such as tumor suppression and immune stimulation.[17,18] Taken together, the risk of secondary malignancies from LD-RT is likely to be very low or negligible and should therefore not be considered a limiting factor is its future use as a treatment option.

Study Limitations

One of the major limitations with comparing hematological changes across the various treatments was the incomplete CBC data sets. The majority of articles did not address all components of a CBC, making it difficult to compare and interpret the data when studies do not report on the same parameters. Another factor that makes it difficult to compare CBC's across studies is the multiple grading scales. There is no standard grading scale for hematologic toxicity, therefore each article may use one of several scales (WHO, CTCAE, ECOG, and SWOG). While these grading scales are similar,

they are not identical making direct comparison difficult. For example, WHO grade 1 may at times be equivalent to CTCAE grade 1, but not always due to the slight variance between grading scale criteria (Table 1). The variability in the patients and cancer type may also have the potential to confound the results. These variables can include age, ethnicity, previous treatments, severity, or type of cancer. To date, the majority of LD-RT studies have focused on patients with lymphoma or leukemia, and leaves possibility for other hematological effects in patients with non-blood-based cancers. It is also important to consider neoadjuvant or concurrent treatments that patients may undergo as each treatment will provide its own set of effects on hematopoiesis. Combination chemo-radiation was covered in this review; however, there are various other combined treatments that can be utilized. The year in which treatments were administered will also impact the comparison of hematological effects. Most LD-RT clinical trials were conducted in the 1960s to 1980s, whereas many of the HD-RT and chemotherapy data are from more recent studies. There have been significant advances in the diagnosis and treatment of cancer patients over the past few decades. Therefore, it is difficult to compare hematological data from studies that were conducted many years apart. On the other hand, studies that are several decades old provide the potential for long-term follow up. While it is important to know how the hematologic system reacts during these treatments, it is also valuable to observe the changes that occur as the body recovers from the cytotoxic nature of cancer treatments. Unfortunately, very few studies report on the long-term effects that these treatments have on hematological parameters. Many of these limitations could be overcome with additional modern clinical trials on LD-RT which accurately document hematological changes and continue to follow patients long-term to evaluate efficacy and toxicity.

Conclusions

Based on the literature reviewed, various hematological toxicities can occur following cancer therapy. Across conventional treatments, chemotherapy and high dose radiation therapy have similar and more widespread impacts on blood counts, in particular leukocytes. However, due to its systemic nature, chemotherapy often causes more adverse effects such as infection and fever, resulting in many hospitalizations for patients. Combination treatment results in increased hematologic toxicity compared to single modality treatments. In general, low dose radiation therapy has less of an effect on blood counts and lower hematologic toxicity when compared to conventional treatments. Clinical trials exploring the effects of LD-RT began over 40 years ago and the mechanisms have been studied in animal models for over 25 years. During this period there has been continuous support of the anti-cancer effects of low dose irradiation in both animal and human studies. The use of LD-RT in cancer treatment could result in better quality of life, and less adverse side effects for patients. Overall, based on the data reviewed here, it does not appear that hematological toxicity is a limiting factor in the applicability of LD-RT.

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