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REVIEW ARTICLE

The Function of Radiotherapy in the Treatment of Leukemia: Review

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ABSTRACT

Radiotherapy has continued to be a significant component of the management of leukaemia as a complementary modality with chemotherapy, targeted therapy and hematopoietic stem cell transplantation (HSCT). It is used in total body irradiation (TBI) as part of conditioning regimens before transplantation, in cranial irradiation in instances of the central nervous system (CNS) involvement and in palliative care in palliative care of the disease. The new changes in the radiotherapy techniques such as intensity-modulated radiotherapy (IMRT) and total marrow irradiation (TMI) have significantly improved the accuracy of treatment which has consequently led to a higher sparing of healthy tissues without affecting the treatment effectiveness. Moreover, new measures like radioimmunotherapy and proton therapy are part of the future of precision medicine and will reduce toxicity and improve the outcome of treatment among other measures. This review gives a general overview of the changing role of radiotherapy in leukaemia focusing on the current role of radiotherapy, technology and future of radiotherapy integration with systemic and targeted therapies.

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1- INTRODUCTION

Blood is a particular connective tissue which achieves vital physiological functions, comprising oxygen transport, nutrient delivery, immune defences, and waste removal. It is poised of plasma and cellular elements for instance white blood cells, red blood cells, and platelets, individually playing a critical role in preserving homeostasis and defensive the body against disease [1, 2]. Interruption of normal hematopoiesis, the process by that blood cells are produced in bone marrow can cause malignant conditions collectively known as haematological cancers [3].

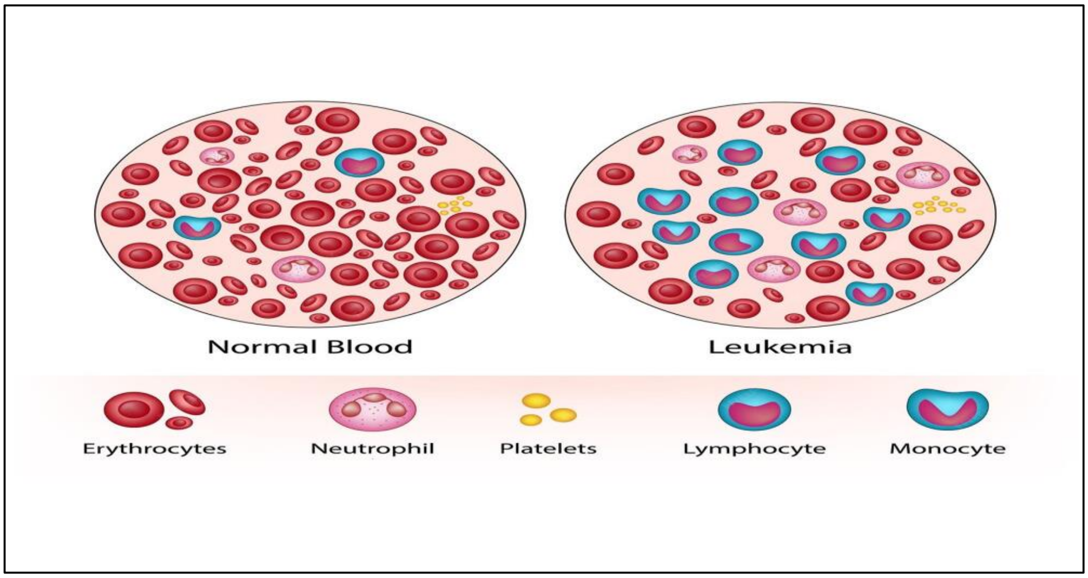

Fig (1): Leukemic and normal blood is compared. Platelets, erythrocytes, monocytes, lymphocytes, and neutrophils are all found in balanced amounts in healthy blood. Leukemic blood, on the other hand, is defined by a higher quantity of abnormal immature WBCs (blasts), interfering with normal hematopoiesis as well as impair physiological function [4]

Leukemia can be defined as a hematological malignancy that is very prevalent and is a condition in which there is uncontrolled growth of abnormal WBCs, which affects the normal immune system by impairing the healthy hematopoietic cells [5]. The World Health Organization (WHO) categorizes leukemia into four broad categories, which include acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), and chronic lymphocytic leukemia (CLL). These subtypes vary in terms of cell lineage (lymphoid or myeloid) and disease progression (chronic or acute), which gives them dissimilar clinical characteristics and treatment strategies [6, 7].

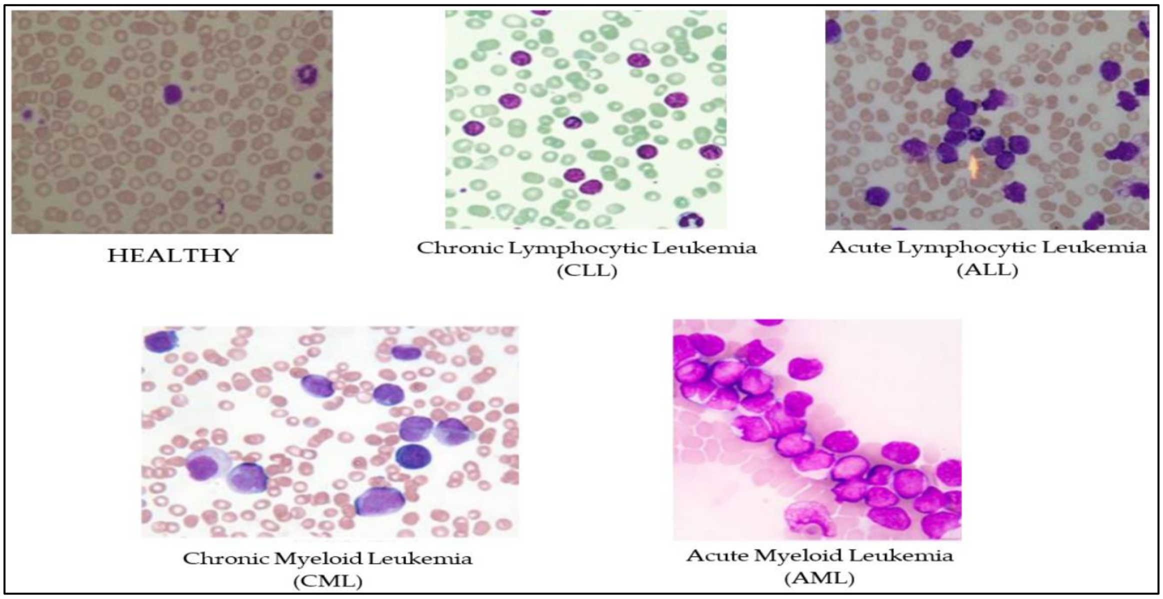

Fig (2): Morphological comparison of normal blood and the four major types of leukemia: (A) Healthy blood, (B) CLL, (C) ALL, (D) CML, and (E) AML [8]

Leukemia is approximately 3% of new cancer cases that are diagnosed, globally, yet its incidence varies with age. Children have a higher likelihood of acute lymphoblastic leukemia, whereas adults and elderly patients have a higher likelihood of AML and CLL [9]. Even though the significant advances have been made in chemotherapy, targeted therapy, and stem cell transplantation, radiotherapy continues to be an essential part of leukemia treatment, particularly in conditioning prior to hematopoietic stem cell transplantation, and in cases involving the involvement of the central nervous system (CNS) [10,11]. The role has also been enhanced by the new advanced modalities like IMRT and TBI, which offer greater treatment accuracy and reduced toxicity [12]. In this review, the topic of radiotherapy in the treatment of leukemia will be discussed on its historical application, its use in the present and its future application regarding newer therapies.

The Role of Radiotherapy in the Treatment of Leukemia

Systemic chemotherapy and HSCT are regarded as the standard of care and radiotherapy is not a first-line treatment in the leukemia condition. Nevertheless, radiotherapy has a significant supportive and specific role in the situation of specific clinical cases. It is used based on disease subtype, tumor burden and the necessity to undergo conditioning regimens prior to transplantation.

1. Total Body Irradiation (TBI)

The best-established applications of radiotherapy in the management of leukaemia are TBI commonly applied in conjunction with high-dose chemotherapy as a conditioning regimen before allogeneic HSCT. TBI eliminates residual leukemic cells, gives extensive immunosuppression for preventing graft-rejection, and enables the engraftment of donor stem cells [13,14]. It is demonstrated that fractionated regimens of TBI are less toxic, like the pulmonary and gastrointestinal damage and retain the anti-leukemic effect [15]. The common regimens of typical TBI are between 10-14 Gy, usually administered in fractionated dosages (e.g. 12 Gy in 6 fractions over 3 days) for reducing toxicity whilst preserving therapeutic efficacy.

2. Central Nervous System (CNS) Prophylaxis and Therapy

CNS infiltration by leukemic cells is common in ALL. Whereas intrathecal chemotherapy is now the treatment of choice, cranial irradiation can still be used with patients who are at very high risk, or with CNS relapse, an option in high-risk patients or in CNS relapse [16,17]. Cranial RT is an effective way to lower the relapse rates, however, with long-term adverse effects especially in neurocognitive decline in children [18]. Present guidelines restrict cranial radiotherapy to relapsed or refractory CNS leukemia.

3. Extramedullary Disease Control

Localized external beam radiotherapy is very useful in reducing the tumor burden, relieving pain, and avoiding functional loss in cases of chloramas (myeloid sarcomas) or other extramedullary leukemic infiltrates [19]. Doses of between 20-24 Gy can be used in most cases to provide lasting local control [20].

4. Palliative Radiotherapy

In the case of advanced or relapsed leukemia, radiotherapy may be utilized in the palliative setting to alleviate bone pain, lymphadenopathy or organomegaly. In such environments, low-dose RT can be effective with very little-toxicity [21].

5. Emerging Techniques: Targeted Radiotherapy

Recent developments include Radioimmunotherapy (RIT) which uses monoclonal antibodies labeled with radionuclides, which target the leukemic cells with radiation. In monoclonal antibodies labeled to radionuclides (e.g. anti-CD33 or anti-CD45), the monoclonal antibodies are used to deliver radiation to the leukemic cells. There are clinical tests that propose RIT to complement conditioning regimens without damaging normal tissues [22,23]. Moreover, proton therapy is also being explored as a means of limiting the amount of radiation reaching normal organs during TBI [24].

The Role of Intensity-Modulated Radiation Therapy (IMRT) in Leukemia

Radiotherapy had been incorporated into the conditioning program of HSCT, and in the treatment of extramedullary leukaemia. The standard forms of TBI methods however expose masses of normal tissues to radiation resulting in serious toxicities. IMRT is a newer form of radiation therapy which enables a high degree of conformal dose distribution, which reduces the amount of irradiation to organs at risk (OARs) yet provides sufficient dose to the target [25].

1. IMRT in Total Body Irradiation (TBI) and Total Marrow Irradiation (TMI)

IMRT has transformed the idea behind TBI by permitting Total Marrow Irradiation (TMI) whereby the amount of radiation is kept to the bone marrow and lymphoid tissues (where leukemic invasion mostly occurs) and sparing important organs like lungs, heart, liver and kidneys [26,27]. IMRT-based TMI has demonstrated during clinical tests to result in; Lower toxicity compared to conventional TBI. Reduced incidence of pulmonary and gastrointestinal complications, and maintenance of effective anti-leukemic activity before HSCT [28,29].

2. IMRT for Extramedullary Leukemia and Sanctuary Sites

IMRT has been noted to be of special use in treatment of extramedullary leukemic lesions (e.g., myeloid sarcoma, CNS involvement, or testicular relapse), as it offers excellent local control without damaging adjacent vital tissues [30].

For example, in cranial or orbital relapses of acute lymphoblastic leukemia (ALL), IMRT can limit radiation dose to the optic nerves and brainstem, thereby reducing the risk of neurocognitive and visual complications [31].

3. Pediatric Applications

Since children with leukemia are especially susceptible to toxicities in the long term, IMRT is being investigated as a means of reducing long-term (late) effects in children. IMRT reduces radiation to developing organs, such as the thyroid, brain, and lungs, by the use of dose distributions, which reduce the risks of secondary malignancies, endocrine dysfunction, and neurocognitive decline [32,33].

4. Clinical Outcomes and Limitations

Despite the preliminary research results of improved toxicity profiles with the use of IMRT; long-term outcome is underway. Some limitations include: Increased treatment planning complexity and cost, Longer delivery times compared to standard TBI, and Uncertainty regarding secondary malignancy risk due to low-dose exposure [34].

The following table summarizes the main differences among the techniques: Total Body Irradiation (TBI), Intensity-Modulated Radiation Therapy (IMRT), Total Marrow Irradiation (TMI), Proton Therapy, and Radioimmunotherapy (RIT).

Table1: Comparative Table of Radiotherapy Techniques in Leukemia Treatment

Technique	Definition	Clinical Use in Leukemia	Advantages	Limitations	Ref
Total Body Irradiation (TBI)	Uniform irradiation of the entire body, typically used as part of conditioning before HSCT.	Eradication of residual leukemic cells and immunosuppression prior to transplantation.	Effective immunosuppression and leukemia control; fractionation reduces toxicity.	Non-specific irradiation of normal tissues; pulmonary, gastrointestinal, and endocrine toxicities.	[12–15,21, 24]
Intensity-Modulated Radiation Therapy (IMRT)	Advanced technique delivering highly conformal dose distributions while sparing organs at	Used in extramedullary lesions and conditioning with reduced toxicity.	Decreased dose to the normal tissues and maintaining the therapeutic efficacy.	Complex planning, longer treatment time, higher cost.	[25,28–31,33, 34]

	risk (OARs).				
Total Marrow Irradiation (TMI)	Selective irradiation of bone marrow and lymphoid tissues and sparing critical organs.	Alternative to TBI in HSCT conditioning with reduced toxicity.	Lower organ toxicity as well as enhanced targeting regarding the leukemic sites.	Requires advanced technology; limited availability.	[25–29]
Proton Therapy	Radiation therapy using protons with Bragg peak properties to reduce exit dose.	Investigational use in TBI/TMI to minimize normal tissue exposure.	Superior normal tissue sparing; potential reduction in late toxicity.	Limited availability, high cost, limited clinical data.	[24]
Radioimmunotherapy (RIT)	Monoclonal antibodies labeled with radionuclides targeting leukemic cells.	Used in conditioning regimens or targeted therapy.	High specificity with reduced systemic toxicity.	Limited clinical data; isotope production challenges.	[22,23]

2- CONCLUSION

The management of leukaemia also involves radiotherapy which is not a first line curative treatment but rather an adjunctive treatment modality that is determined by the specific clinical setting. The morbidity of treatment and the maximization of disease control are the trade-offs that are brought out by its evolving role. The shift to the precision medicine in the area of hematologic oncology is emphasized by the incorporation of new technologies, such as IMRT, TMI, and radioimmunotherapy. The future directions should be geared towards optimization of the dose delivery, patient selection and combination of radiotherapy with other new systemic therapies to enhance the chance of survival without aggravating the quality of life.

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