

THERANOSTICS IN HEMATOLOGIC MALIGNANCIES: ADVANCES, CHALLENGES, AND FUTURE PROSPECTS

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Article Received on
30 July 2025,

Revised on 20 August 2025,
Accepted on 10 Sept. 2025

DOI: 10.20959/wjpr202518-38334



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ABSTRACT

The advent of personalized medicine has significantly reshaped the management of hematologic malignancies such as leukemias, lymphomas, and myelomas. One of the most impactful innovations in this field is theranostics an approach that integrates diagnostic and therapeutic strategies within a unified framework. By combining advanced molecular imaging with targeted therapies, theranostics facilitates more accurate disease characterization and patient-tailored treatment, ultimately improving outcomes while reducing treatment-related toxicity. Conventional therapeutic options, including chemotherapy, radiotherapy, and stem cell transplantation, though widely used, are often limited by systemic side effects and the risk of resistance. Theranostic approaches overcome these challenges by employing genetic and molecular profiling to personalize treatment, thereby minimizing harm to normal tissues and enhancing therapeutic efficacy. Key advancements include molecular imaging, radio immunotherapy, and the development of targeted theranostic agents. Molecular imaging enables visualization of disease at a cellular and molecular level, improving both diagnostic precision and treatment monitoring. Radio immunotherapy combines monoclonal antibodies with radiolabeled isotopes to selectively eliminate malignant cells

while sparing healthy tissues. Similarly, novel theranostic agents are being engineered to deliver therapeutic compounds directly to cancer cells, reducing off target effects and optimizing response. Current research and clinical trials continue to explore these strategies, focusing on refining imaging technologies, improving targeted agents, and assessing long-term safety and efficacy. Collectively, theranostics represents a paradigm shift in hematologic oncology, with the potential to transform cancer care by advancing precision medicine, reducing adverse effects, and enhancing patient survival and quality of life.

KEYWORDS: Leukemias, Lymphomas, Myelomas, Molecular Imaging and Theranostic Agents.

INTRODUCTION

Over the last decade, the field of medicine has evolved rapidly, driven by advances in technology and an increased understanding of human biology at the molecular level. Central to this progress is the shift towards personalized and integrated treatment approaches, which have the potential to revolutionize the management of various diseases, particularly cancers. Personalized medicine aims to tailor healthcare to individual characteristics, such as a person's genetic profile, and is fundamentally transforming how diseases are diagnosed, treated, and prevented. One of the most promising innovations in this area is theranostics, a paradigm that combines diagnostic and therapeutic processes into a single, streamlined approach, enabling more precise and effective patient care.^[1]

Hematologic malignancies encompass a range of complex cancers, including leukemias, lymphomas, and myelomas, each presenting unique challenges in treatment due to their diverse nature. Originating in the blood, bone marrow, and lymphatic system, these cancers exhibit significant biological variability, which contributes to a wide spectrum of clinical presentations and responses to therapy. Leukemias, characterized by the uncontrolled proliferation of blood cells in the bone marrow, can manifest in acute or chronic forms, each with distinct progression patterns and treatment responses. Acute leukemias, such as acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), often require aggressive treatment strategies due to their rapid onset and progression. Chronic leukemias, like chronic lymphocytic leukemia (CLL) and chronic myeloid leukemia (CML), generally develop more slowly but can still present significant treatment challenges. Lymphomas, which arise from the lymphatic system, are broadly categorized into Hodgkin lymphoma and non-Hodgkin lymphoma (NHL). Hodgkin lymphoma, marked by the presence of Reed-Sternberg cells,

tends to have a more predictable progression and often responds well to conventional therapies. Non-Hodgkin lymphoma, however, encompasses a diverse group of malignancies with varying histologies and clinical behaviors, making treatment decisions more complex. Myelomas, specifically multiple myeloma, involve the abnormal proliferation of plasma cells in the bone marrow. This cancer can lead to various complications, including bone lesions, anemia, and kidney dysfunction. The treatment of multiple myeloma often involves a combination of chemotherapy, targeted therapies, and immunotherapy. The heterogeneity of hematologic malignancies necessitates a personalized approach to treatment, as responses can vary widely among patients. Advances in understanding the molecular and genetic underpinnings of these cancers have led to the development of more targeted therapies and precision medicine strategies. Despite these advances, the complexity of these diseases means that managing and treating hematologic malignancies remains a significant challenge, requiring ongoing research and innovation to improve outcomes and patient quality of life.^[2]

Traditional treatments like chemotherapy and radiotherapy are often used in a standard way for many patients, but they don't always work well for everyone. These treatments are designed to attack rapidly growing cancer cells or use radiation to damage them, but they don't account for the specific genetic makeup of each patient's cancer. Because each cancer can have different genetic mutations and characteristics, these generalized methods may not be effective for all individuals. Personalized medicine seeks to improve treatment outcomes by tailoring therapies to the unique features of each patient's disease. This approach starts with analyzing the cancer cells to understand their specific genetic and molecular profiles. With this detailed information, doctors can choose treatments that target the exact mutations or pathways driving the cancer. For instance, if a tumor has a specific mutation, doctors might use targeted drugs designed to attack cells with that mutation while sparing healthy cells, leading to better results and fewer side effects. Additionally, personalized medicine includes advances like immunotherapy, which helps the immune system recognize and destroy cancer cells more efficiently. By identifying particular antigens or markers on the cancer cells, immunotherapy can be tailored to each patient's cancer, enhancing the effectiveness of the treatment. In practice, personalized medicine means doctors consider not only the cancer's genetic details but also the patient's overall health, lifestyle, and preferences. This comprehensive approach ensures that treatment plans are customized to fit the individual's specific needs and circumstances. With ongoing research and technological advances, personalized medicine is evolving to become more precise. The integration of

genetic data with sophisticated computational tools allows for the creation of highly individualized treatment plans. This shift from a one-size-fits-all approach to a more tailored strategy aims to improve patient outcomes, reduce unwanted side effects, and offer more effective care. As the field continues to grow, personalized medicine holds the promise of transforming how various diseases, including cancer, are treated, ultimately leading to more successful and targeted therapies.^[3]

Theranostics is emerging as a critical tool in the management of hematologic malignancies, offering a more individualized approach to treatment. This field leverages advanced diagnostic technologies, such as molecular imaging and biomarker analysis, to gain a deeper understanding of the disease at the molecular level.^[4] For instance, positron emission tomography (PET) scans using specific imaging agents can accurately visualize the extent of disease and monitor treatment response in real-time.^[5]

Such precise imaging is essential for formulating targeted therapeutic strategies, which can be tailored to the specific characteristics of the malignancy. One of the most groundbreaking aspects of theranostics is its ability to deliver targeted therapy directly to cancer cells, minimizing damage to healthy tissues and reducing side effects.^[6] Radio immunotherapy, for example, involves the use of monoclonal antibodies conjugated with radioactive isotopes that specifically target cancer cells. Upon binding to the cancer cells, these isotopes deliver a lethal dose of radiation, effectively killing the malignant cells while sparing surrounding healthy tissues.^[7] This precision medicine approach not only enhances the efficacy of the treatment but also improves the patient's quality of life by reducing the side effects commonly associated with conventional therapies. What sets theranostics apart from other treatment approaches is its ability to integrate diagnosis and therapy into a cohesive process. This integration allows for continuous monitoring of treatment efficacy, enabling real-time adjustments to therapy based on the patient's response.^[8] This feedback loop is crucial for optimizing treatment outcomes, particularly in diseases as complex as hematologic malignancies. By combining precise diagnostics with targeted therapies, theranostics offers a more responsive and adaptable approach to cancer treatment.

Theranostics represents a groundbreaking advancement in the treatment of hematologic malignancies, offering a more personalized, effective, and less invasive approach compared to traditional therapies. By integrating diagnostic and therapeutic processes, theranostics enhances the precision of medical interventions and significantly improves patient outcomes.

This innovative field bridges the gap between diagnosis and treatment, tailoring therapies to the individual characteristics of each patient's disease. As theranostics continues to develop, it promises to further revolutionize cancer treatment, making personalized medicine increasingly accessible to patients worldwide. The fusion of advanced diagnostic techniques with targeted therapies marks not only a technological leap but also a profound shift in modern medicine. This paradigm shift offers renewed hope and potential for millions affected by these challenging diseases, driving progress towards more effective and customized treatment options.

Traditional Therapies for Hematologic Malignancies and their Disadvantages

Hematologic malignancies represent a diverse group of cancers originating from blood cells and lymphatic tissues. These include leukemias (e.g., acute myeloid leukemia, chronic lymphocytic leukemia), lymphomas (e.g., Hodgkin lymphoma, non-Hodgkin lymphoma), and multiple myeloma. These malignancies are characterized by abnormal proliferation of hematopoietic cells and often involve complex disease mechanisms. Traditional therapies, including chemotherapy, radiation therapy, and stem cell transplantation, have played a crucial role in the management of these diseases for decades. Chemotherapy, radiation, and stem cell transplantation each have distinct mechanisms and indications, tailored to different types of hematologic malignancies. For instance, chemotherapy is often used for aggressive leukemias and lymphomas, while radiation therapy is typically reserved for localized disease or as part of a combination regimen. Stem cell transplantation offers a potential cure for patients with relapsed or refractory disease but comes with its own set of complications. Despite their success, traditional therapies are not without significant drawbacks. These include severe side effects, development of resistance, and long-term toxicities that can affect patients' overall health and quality of life. As we continue to advance in understanding the molecular and genetic underpinnings of hematologic malignancies, there is a growing need to address these limitations and explore new therapeutic options.^[9-10]

Chemotherapy

Chemotherapy involves the use of cytotoxic drugs to kill cancer cells or inhibit their proliferation. These drugs target rapidly dividing cells, which includes most cancer cells but also some normal cells, leading to a range of side effects.

Commonly used chemotherapy agents for hematologic malignancies include

Cytarabine: Often used for acute myeloid leukemia (AML) and certain types of lymphomas. It inhibits DNA synthesis by mimicking cytidine, a DNA building block.

Daunorubicin: A topoisomerase II inhibitor used in the treatment of acute leukemia. It interferes with DNA replication and transcription.

Etoposide: Another topoisomerase II inhibitor, effective in various types of leukemia and lymphoma.

Despite their effectiveness, these drugs have significant drawbacks

Non-specificity: Chemotherapy drugs are not selective for cancer cells alone; they also target normal, healthy cells that are rapidly dividing. This lack of specificity results in a range of adverse effects.

Chemotherapy commonly causes

Gastrointestinal Toxicity: Nausea, vomiting, and diarrhea are prevalent due to the effects on the gastrointestinal epithelium.

Hematologic Toxicity: Myelosuppression leading to anemia, neutropenia, and thrombocytopenia increases the risk of infections, bleeding, and fatigue.

Alopecia: Hair loss is a distressing side effect affecting patients' appearance and self-esteem.

Resistance Mechanisms: Cancer cells can develop resistance to chemotherapy over time. This resistance can be mediated through several mechanisms:

Drug Efflux Pumps: Proteins like P-glycoprotein can pump chemotherapy drugs out of cancer cells, reducing their efficacy.

Target Mutations: Mutations in the targets of chemotherapy drugs, such as topoisomerases, can render the drugs less effective.

Enhanced DNA Repair: Increased activity of DNA repair enzymes can counteract the damage caused by chemotherapy.

Resistance leads to treatment failure and relapse, making management of the disease more challenging.

Quality of Life Issues: Long-term chemotherapy use can result in chronic health problems:

Cognitive Impairment: Patients may experience "chemo brain," characterized by cognitive difficulties such as memory loss and concentration problems.

Fertility Issues: Chemotherapy can cause infertility, particularly in younger patients, affecting their future quality of life.

Secondary Malignancies: Long-term survivors are at increased risk of developing secondary cancers, such as leukemia or solid tumors, due to the mutagenic effects of chemotherapy¹¹⁻¹².

Radiation Therapy

Radiation therapy uses high-energy radiation to target and kill cancer cells. It can be delivered externally using a linear accelerator or internally using radioactive implants. Radiation therapy is often employed in the treatment of localized hematologic malignancies, such as Hodgkin lymphoma or certain types of non-Hodgkin lymphoma. Radiation is effective in shrinking tumors and treating areas with residual disease after chemotherapy. However, its use is associated with several limitations.

Disadvantages

Acute side effects occur during or shortly after radiation therapy and can include:

Skin Irritation: Patients may experience redness, dryness, or ulceration in the irradiated area.

Mucositis: Inflammation of mucous membranes can lead to painful sores in the mouth, throat or gastrointestinal tract.

Fatigue: A common side effect that can significantly impact daily activities and overall quality of life.

Long-term complications of radiation therapy include

Secondary Cancers: Patients treated with radiation are at increased risk of developing secondary cancers, such as breast cancer or thyroid cancer, depending on the irradiated site.

Endocrine Dysfunction: Radiation to areas like the neck or chest can cause long-term issues such as hypothyroidism or growth hormone deficiency.

Organ Damage: Radiation can cause permanent damage to organs near the treatment area, such as lung fibrosis or cardiac issues.

Effectiveness in Disseminated Disease: Radiation therapy is primarily effective for localized disease. For widespread or disseminated disease, radiation alone is usually inadequate and must be combined with other treatments. Its limited scope in treating systemic disease highlights its role as part of a multimodal treatment strategy rather than a standalone option.^[13-14]

Stem Cell Transplantation

Stem cell transplantation involves replacing damaged or diseased hematopoietic cells with healthy stem cells. This can be done via autologous transplantation (using the patient's own cells) or allogeneic transplantation (using cells from a donor). Stem cell transplantation is often used for patients with high-risk or relapsed hematologic malignancies, offering a potential cure or long-term remission.

Disadvantages

Graft-Versus-Host Disease (GVHD)

GVHD is a serious complication of allogeneic stem cell transplantation, where the donor's immune cells attack the recipient's tissues.

Acute GVHD: This can occur within the first 100 days post-transplant and may affect the skin, liver, and gastrointestinal tract. Symptoms include rash, jaundice, and diarrhea.

Chronic GVHD: This can develop later and lead to long-term complications such as fibrosis, sclerodermatous changes, and chronic mucosal damage.

Management of GVHD often involves immunosuppressive medications, which can further increase the risk of infections and other complications.

Infectious Risks

Patients undergoing stem cell transplantation are highly susceptible to infections due to:

Neutropenia: Chemotherapy and radiation used in the conditioning regimen can severely reduce white blood cell counts, increasing infection risk.

Immunosuppressive Therapy: Medications used to prevent GVHD also impair the immune system, making patients vulnerable to a range of infections, including bacterial, viral, and fungal pathogens.

Preventive measures, such as prophylactic antibiotics and antifungals, are essential but do not completely eliminate the risk of infections.

Long-term Toxicities

Survivors of stem cell transplantation may face

Organ Dysfunction: Long-term effects can include lung damage, cardiac issues, and hepatic dysfunction.

Endocrine Problems: Disorders such as hypothyroidism, adrenal insufficiency, or infertility can arise.

Psychosocial Issues: The emotional and psychological impact of the transplant and its long-term effects can significantly affect survivors' quality of life.^[15]

Theranostic Approaches in Hematologic Malignancies

Theranostics represents an innovative approach that merges diagnostics and therapeutics, aiming to provide a tailored treatment plan for individual patients. This integrated strategy enhances the precision of medical interventions by using diagnostic tools to identify specific disease markers and guide therapy. In hematologic malignancies, theranostics has become a transformative approach, leveraging advances in molecular biology, imaging technology, and targeted therapy to improve patient outcomes. Historical context includes the evolution from traditional diagnostic and therapeutic methods to modern, integrated approaches that allow for real-time monitoring and adjustment of treatments based on patient-specific data.^[16]

Molecular Targets in Hematologic Malignancies

Molecular targets in hematologic malignancies include surface antigens, receptors, and intracellular signaling pathways critical for the survival and proliferation of cancer cells. For instance, CD19 is a prominent target in B-cell malignancies, while CD20 is targeted in various lymphomas. Additionally, tyrosine kinases (e.g., BCR-ABL in chronic myeloid leukemia) and mutations in genes like FLT3 or IDH1/2 in acute myeloid leukemia are crucial targets. This section details how identifying and validating these targets through genomic and proteomic analyses can lead to the development of targeted theranostic agents that selectively attack cancer cells while sparing normal tissue.^[17]

Theranostic Agents in Hematologic Malignancies

Theranostic agents encompass a variety of compounds, including monoclonal antibodies conjugated with radioactive isotopes or cytotoxic drugs, bispecific antibodies, and small molecules with diagnostic and therapeutic functions. For example, the anti-CD20 monoclonal antibody rituximab, combined with the radioisotope Y-90, is used in the treatment of non-Hodgkin lymphoma. Similarly, radio immuno conjugates like ibritumomab tiuxetan offer targeted radiation therapy. This section reviews the development process of these agents, their mechanisms of action, and their clinical effectiveness. Additionally, it explores how these agents are designed to minimize off-target effects and enhance therapeutic efficacy.^[18]

Diagnostic Imaging Techniques

Diagnostic imaging plays a crucial role in theranostics by providing detailed information about the distribution, uptake, and efficacy of therapeutic agents. PET imaging, using radiotracers like ^{18}F -FDG, allows for the assessment of metabolic activity and disease progression. SPECT imaging, often combined with radiolabeled antibodies, helps in tracking the localization of therapeutic agents. MRI provides high-resolution images of tissue structure and can be used in conjunction with contrast agents to enhance visibility of tumor lesions. This section discusses the advantages and limitations of each imaging modality and their applications in monitoring patient response to theranostic interventions.^[19]

Combination Therapies

Combining theranostic approaches with other therapeutic modalities, such as chemotherapy, immunotherapy, and targeted therapy, can enhance overall treatment efficacy. For example, combining CAR-T cell therapy with theranostic imaging allows for precise targeting and monitoring of CAR-T cells *in vivo*. Additionally, the use of theranostic agents alongside traditional chemotherapy can help in identifying patients who are most likely to benefit from specific drugs, thus optimizing treatment regimens. This section reviews various combination strategies, their clinical evidence, and how they contribute to improved treatment outcomes for patients with hematologic malignancies.^[20]

Patient Selection and Personalized Medicine

Personalized medicine is pivotal in theranostics, as it involves tailoring treatment based on individual patient characteristics, including genetic, molecular, and clinical factors. Techniques such as next-generation sequencing (NGS) and molecular profiling are used to identify specific biomarkers and mutations that guide the selection of appropriate theranostic agents. This section elaborates on how personalized approaches improve treatment outcomes by ensuring that patients receive the most effective therapies based on their unique disease profiles. It also discusses how advancements in genetic and molecular diagnostics contribute to the precision of theranostic strategies.^[21]

Clinical Trials and Outcomes

Clinical trials are essential for evaluating the safety and efficacy of theranostic approaches. This section reviews recent major trials, including study designs, patient populations, and primary and secondary endpoints. Trials like those evaluating the efficacy of Y-90 ibritumomab tiuxetan or CAR-T cell therapies provide insights into how theranostic agents

perform in real-world settings. The section also covers trial outcomes, including response rates, progression-free survival, and overall survival, and discusses how these findings impact clinical practice and future research.^[22]

Safety and Adverse Effects

Theranostic agents, while beneficial, can also pose risks and adverse effects. This section examines common and severe side effects associated with these agents, such as myelosuppression, infusion reactions, or off-target toxicity. It discusses strategies for managing these adverse effects, including premedication, dose adjustments, and supportive care. Furthermore, it reviews ongoing research focused on improving the safety profiles of theranostic agents and minimizing the incidence of adverse reactions.^[23]

Future Directions and Innovations

The field of theranostics is rapidly evolving with innovations in drug development, imaging technology, and molecular diagnostics. This section explores emerging trends such as the development of novel radiolabeled compounds, advancements in high-resolution imaging, and the integration of artificial intelligence in data analysis. It also discusses potential future breakthroughs, such as next-generation theranostic agents with improved specificity and efficacy. Challenges such as regulatory hurdles and the need for extensive validation are also addressed.^[24]

CONCLUSION

Theranostics represents a transformative advancement in the treatment of hematologic malignancies, bridging the gap between diagnosis and therapy through its innovative approach. By leveraging cutting-edge diagnostic tools and targeted therapeutic agents, this integrated strategy enhances the precision and personalization of cancer treatment, aiming to improve patient outcomes and quality of life. Traditional methods, while effective, often come with significant drawbacks, including severe side effects and treatment resistance. Theranostics offers a promising alternative by tailoring interventions to the individual genetic and molecular profiles of patients, thus reducing harm to healthy tissues and optimizing therapeutic efficacy. As research and technology continue to evolve, the ultimate goal of theranostics is to refine these approaches further, making personalized, effective cancer care increasingly accessible and revolutionizing the landscape of oncology.

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