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Key Inforbits

- September is Blood Cancer AAwareness Month!
- Refreshers on current treatments for hematologic malignancies
- Three major blood malignancies?
- Recent FDA approvals related to hematology and therapies in the works causing a buzz!

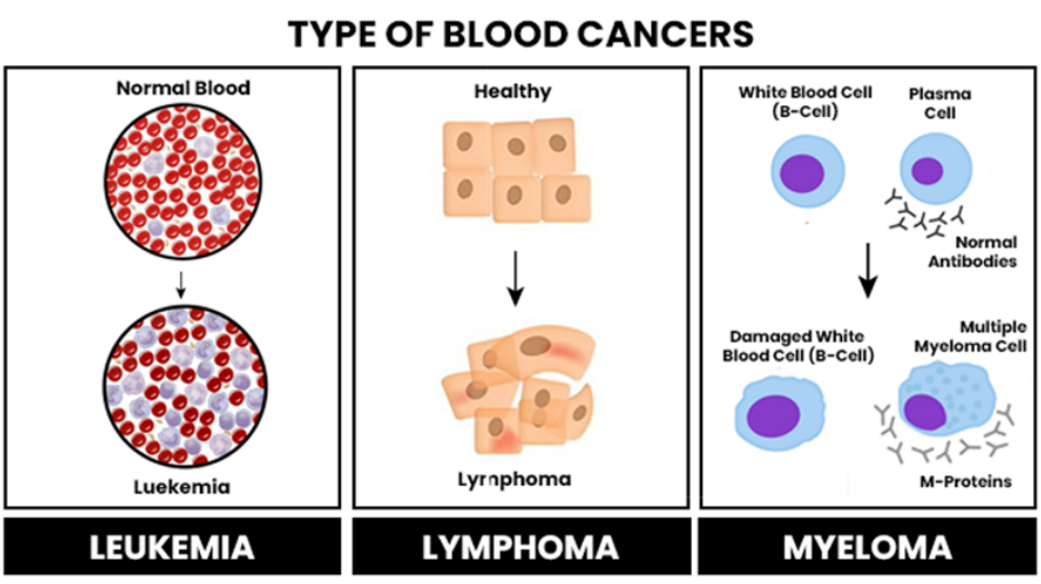
September is Blood Cancer Awareness Month

Background:

To support Blood Cancer Awareness month, this issue will focus on the three major types of hematologic malignancies, how they are categorized, occurrence rates specific to each, current treatment methods and the current buzz around oncology.

Blood Malignancies:

There are three major cancer subcategories with hematologic origins that can be grouped into one major "blood" malignancy category - these include: leukemias, lymphomas, and myelomas.[1] Each of these malignancies is brought about through mutations in specifics cells in the hematopoiesis cascade, and are divided once more based on a myriad of factors.



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Leukemias:

Leukemias emerge due to unregulated and/or dysfunctional leukocyte proliferation. They can be categorized into primary or secondary leukemia based on origin of abnormal leukocyte production (cancer vs. medication-induced) and are subdivided into various categories based on cellular origin (myeloid or lymphoid) and whether malignancy is acute or chronic – the latter is dependent on characteristics of proliferating cells (more differentiated/mature vs. undifferentiated), cellular proliferation time (fast vs. slow rate), patient presentation and treatment response. [2,3]

The most common leukemia diagnoses include:

1. Acute lymphoblastic leukemia (ALL).
2. Acute myeloid leukemia (AML).
3. Chronic lymphocytic leukemia (CLL).
4. Chronic myeloid leukemia (CML).

Lymphomas:

Lymphoma malignancies arise through mutations of cells from lymphatic tissue.[4] Lymphomas can be categorized broadly into either Hodgkin lymphoma (HL) or non-Hodgkin lymphoma (NHL). Both HL and NHL are subdivided further with HL having either classical or non-classical origin, and NHL as having either B-cell, T-cell or a natural killer cells origin.[5] Classical HL is even further subdivided into four different types, nodular sclerosis, mixed cellularity, lymphocyte rich, and lymphocyte depleted.[5]

A major hallmark of tumors in the "classical" HL category is their composition, as they are predominantly made of mature B-cell based masses which are either small and mononucleated (Hodgkin cells) and large mono and/or multinucleated (Reed-Sternberg cells).[4] Non-classic HL is also referred to as nodular lymphocyte-predominant Hodgkin lymphoma, and as the name implies, afflicted cells in the non-classical category are composed predominantly of nodular lymphocytes.[5]

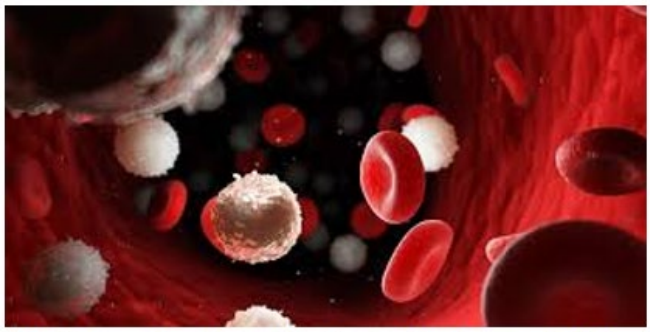
Myelomas:

Myelomas, or to be more precise plasma cell neoplasm malignancies, include multiple myeloma (MM), also referred to as systemic plasma cell neoplasm, and solitary plasmacytoma (a possible antecedent to MM). As the name alludes, the cellular origin in these malignancies are plasma cells such as immunoglobulin-producing B lymphocytes.[6] Solitary plasmacytoma can be subdivided into either solitary plasmacytoma of bone or extramedullary plasmacytoma. The former presenting as a lytic plasma cell lesion on solitary portion of bone tissue and the latter being an isolated plasma cell tumor on soft tissue – usually in soft tissue of the airway.[6]

To note, there is a third condition also involving plasma cell erratic proliferation which may not be malignant earlier on, but which may progress into such a stage – this is monoclonal gammopathy of undetermined significance (MGUS).[6] As a general rule, MGUS (given its nonmalignant status) is less severe than either kind of plasmacytoma and these in turn are less severe than MM.[7]

Occurrence Rates:

Regarding the aforementioned malignancies, the American Cancer Society Cancer Statistics for 2023 estimated 59,610 new cases of leukemia, 89,380 new cases of lymphoma, and 35,730 new myeloma cases. In spite of these alarming numbers, leukemias and lymphoma types have shown various degrees of decreased incidence rates this decade when compared to the previous decade.[8]



https://prognoshealth.com/blog/slowing-blood-cancer-in-its-tracks

Though new case estimations (as well as death estimations) have shown improvements over previous years, each malignancy continues to follow specific patterns and trends throughout.[9,10,11,12] For instance, leukemia shows a higher incidence rate in children aged birth to 14 years old (28% of cases as of 2023) with an 88% 5-year survivability, when compared with the other two malignancies. Furthermore, among the four leukemias mentioned, AML has the lowest rate of occurrence (4%) as well as the lowest 5-year survivability rate.[8]

In the case of lymphomas, Hodgkin lymphoma makes up <1% of all cancers seen in the United States. It has a bimodal distribution onset, presenting itself in early adulthood and then again (though not as predominantly) after the age of 50. It has also been seen to afflict men more so than women, though only slightly so. In spite of this, it does have one of the most curable rates of all cancers with 80% of patients treated achieving remission.[14] Unlike Hodgkin lymphoma, non-Hodgkin lymphomas have a higher rate of occurrence in the United States (4%). As well as a higher occurrence in older populations, with 67 years being the average age of diagnosis. Like Hodgkin lymphoma, non-Hodgkin also occurs more in men than women, though at a comparatively much higher rate.[14]

As far as multiple myeloma is concerned, global statistics showed an increased trend from 1990 to 2016. Current data reports that this trend has remained unchanged.[13,15] It occurs more in men than women and the older adult population with 69 years the average age of diagnosis. Lastly, it is twice as prevalent in the Black population than in the White.[14,15]

Standard Treatments for Hematological Malignancies in Adults:

	Leukemias	Lymphomas	Myelomas
Goal of Treatment	**ALL/AML:** Complete clinical and hematologic remission. **CML:** Eradicate the malignancy from the bone marrow without causing toxicity; cure if possible. **CLL:** Achieve/maintain remission.	Relieve symptoms and achieve cure.	Prolong the patient's survival and improve quality of life.

Standard Drug Therapy	**ALL:** Typical four drug induction regimen includes an anthracycline, vincristine, an asparaginase, and a corticosteroid. **AML:** Standard regimen combines daunorubicin (anthracycline) and cytarabine (antimetabolite). Patients who are Philadelphia chromosome positive also receive targeted therapy with a BCR-ABL tyrosine kinase inhibitor (imatinib, dasatinib, bosutinib, nilotinib). **CML:** Hematopoietic stem cell transplantation (HSCT) is the only proven treatment to cure CML. Other therapies utilized are Interferon Alpha (IFN-a) and BCR-ABL tyrosine kinase inhibitors. **CLL:** Stages 2-4 are treated using a variety of medications, including chemotherapy with aklyating agents or purine analogs, biologic therapy, and targeted therapy.	**HL:** Utilizes combo chemotherapy regimens • ***ABVD***: doxorubicin (Adriamycin), bleomycin, vinblastine, dacarbazine. • ***BEACOPP***: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine (Oncovin), procarbazine, prednisone. • ***A-AVD***: Adcetris (brentuximab vedotin), doxorubicin, vinblastine, dacarbazine. **NHL:** Utilize combo chemoimmunotherapy regimens with/without biologic therapy (can also use single agents). Commonly used 1st line regimens: • R-CHOP or CHOP: rituximab,, cyclophosphamide, doxarubicin, vincristine, prednisone. • BR: bendamustine and rituximab.	**MM:** Standard treatment is the utilization of a three-drug regimen. There are four different types of three-drug regimen utilized consisting of dexamethasone, an immunomodulatory agent, and a proteasome inhibitor. The preferred treatment option is known as VRd. It consists of: • Bortezomib • Lenalidomide • Dexamethasone
Additional Comments	Some unfavorable prognoses for the different leukemia types include: • ***Philadelphia chromosomal translocation*** – which results in tumor cells being protected from induced apoptosis.	***"B – symptoms"*** (occurring in 40% of NHL patients) include: • ***Fever*** • ***Weight loss*** • ***Night sweats*** The R in R-CHOP (***Rituximab***) requires pretreatment with	• ***Bortezomib*** is given subQ in a three-dose regimen given one week apart (day 1, 8 and 15 of treatment). It can also induce neuropathy. • ***Lenalidomide*** capsules must be

	• ***T-cell ALL*** – highly aggressive leukemia. • **MLL rearrangement AML** – Fast onset, highly aggressive, with very poor outcomes. • ***Hypodiploidy*** – rare genetic condition often in ALL with extremely poor outcomes.	acetaminophen and diphenhydramine.	given with water. It is dosed once daily for a 21-day period. • ***Dexamethasone*** is often given in the morning and it is recommended to give with food or after meals. It is given once weekly on day 1, 8, 15 and 22 of treatment.

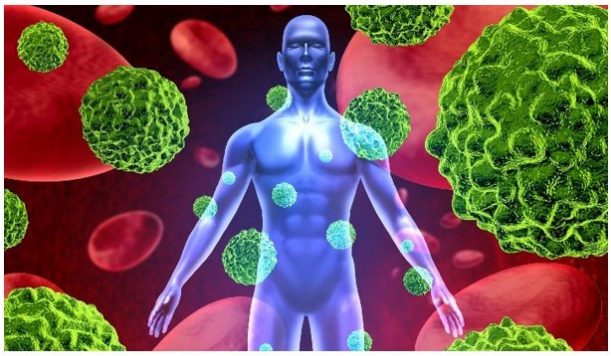
Pharmacological News Related to Treatments:

Since June 2023, three new hematologic malignancy drug therapies have received FDA approval![16] The first of these is ***glofitamab-gxbm (Columvi)*** approved on June 15. Glofitamab-gxbm is designed to treat diffuse large B-cell lymphoma (DLBC), and joins the third therapy to treat DLBC since the beginning of 2023. Glofitamab-gxbm is a monoclonal antibody that targets immune T cells (specifically their CD3 protein) as well as the CD20 transmembrane protein on cancerous cells, enabling a more selective cancer killing mechanism. Its role in therapy is to be used after two or more therapies have been utilized.[17]

The second therapy, ***quizartinib (Vanflyta)***, was approved on July 20.[16] Quizartinib is to be used in treatment for patients with newly diagnosed AML in the face of FLT3 internal tandem duplication or FLT3-ITD – a genetic mutation that carries a poor treatment outcome.[18]

The third and most recent agent to receive FDA approval is ***elranatamab-bcmm (Elrexfio)***, being approved as early as August 14.[16] Elranatamab-bcmm is designated to treat adult patients who have received four various agents and who present with either relapsed or refractory MM.[16,19] All three novel agents will provide eligible patients with a much needed improved chance for survival in their respective diagnoses.

Future Therapies:



https://www.nfcr.org/blog/7-facts-need-know-blood-cancers/

For future therapies, one of the agents which has generated a stir of curiosity in chemotherapy research is a compound known as AOH1996. What makes the compound so promising is that although it is currently in phase I clinical trials, AOH1996 has shown to not only selectively target malignant tumor cell proliferation but it also failed to induce toxicity during small animal testing when given at doses 6 times higher than that required for efficacy. This may make it a much safer and more precise treatment option.[20]

AOH1996 exerts its effect by targeting proliferating cell nuclear antigen (PCNA). PCNA itself has a variety of roles – to include DNA synthesis and repair, chromatin remodeling, and sister chromatid binding. In cells, AOH1996 binds to and stabilizes the bond between PCNA and the largest subunit of RNA polymerase II resulting in its degradation – this interaction is what leads to its selectivity.[20]

However, Dr. Dorothy Bennett, Director of Molecular and Clinical Sciences Research Institute at St. George's University of London remains unconvinced and stated that claims for AOH1996's cancer killing capabilities appear "somewhat limited, disappointingly." Still, Dr Bennet pointed out that, "there appears to be a broad evidence here for retardation of growth (in vitro) of many human cancer cell lines of various types by this agent, with little damage to several normal cell types."[21]

As AOH1996 makes its way through the New Drug Application gauntlet and other therapies continue to receive FDA approval, one thing is certain, though not one person is pleased to hear they've just been diagnosed with cancer, outcomes look more and more promising in the ever evolving world of oncology pharmaceuticals.

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The last "dose"

It is an emotionally taxing odyssey to travel alongside a loved one as they navigate their way through their cancer diagnosis. It is heart wrenching to witness the physical deterioration, and the harsh reality that might be as therapy and disease edges them closer and closer to the precipice. For some of us, that is as close as they get – we see them tiptoe the edge of mortality only to return relatively safe. For others, we watch silently as they fall leaving memories of what was and wishes of what could have been. Regardless of the outcome, the reality is that the love they felt from your presence, from your support during their journey, is just as impactful as the therapy itself. In some cases, even more so. It is this love made manifest in words and deeds that will ferry them through the ordeal, and it will be the thing to ferry you if they do not return. *GAT*

After all, "cancer cannot cripple love; it cannot shatter hope, it cannot conquer the spirit." [Rachel Binford, What Cancer Cannot Do, Cancer Pathways, 2011 October 20.
https://cancerpathways.org/essay/what-cancer-cannot-do/]

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