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original research

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INTRODUCTION

Armenia is a small, upper-middle-income country[1]. It has a population of 2.98 million people; 98.1% are Armenians[2,3]. Most of the population is urban (67.4%), with the largest predominance of residents concentrated in the capital Yerevan (almost 1.1 million people)[2].

Armenia has a decentralized healthcare system that is funded by general taxation. The system consists of three principal tiers: national or republican, regional, and municipal or community[4,5]. State health services offer complimentary or subsidized healthcare, nevertheless, the basic benefits package is underfunded because of the low public budget for health, and the predominant share of healthcare expenses is borne by individuals through out-of-pocket payments, constituting a range from 78% to 85% of total health expenditures during the period 2017-2020[4,6]. Since 2019, there has been a steady increase in coverage of services in Armenia, attributed to a rise in the health budget, and the country is making con-

certed efforts to attain universal health coverage, with a particular focus on expanding the basic benefits package[4,6]. The national health insurance program provides coverage for public health services, primary care, obstetric and postnatal care for all women and newborns, as well as medical services for special-status social groups such as people with special needs, children under 7, children under 18 without parental care, and military personnel. It also covers emergency resuscitation services, medical care for socially significant conditions like tuberculosis and HIV/AIDS, and partial coverage for other conditions, including cancer. Other sources of health financing in Armenia include voluntary health insurance and charitable foundations[7,8].

This nationwide review is based on published national and international literature and expert opinion. Epidemiological data in the current review were collected from the registry of blood diseases at the Yeolyan Hematology and Oncology Center and the National Center of Oncology (NCO), two government-owned medical centers that diagnose and provide care to patients with hematological malignancies in our country. This article aims to offer a comprehensive account of the status of hematologic oncology in Armenia, encompassing aspects such as epidemiology, diagnosis, management, and advancements, as well as identifying challenges and future perspectives. The review will mainly focus on hematologic oncology in adults.

DISCUSSION

Infrastructure and workforce

Hematological malignancies are mainly managed at Yeolyan Hematology and Oncology Center (formerly known as Hematology Center after Prof. R. H. Yeolyan), the only hematology center in Armenia. Rarely lymphoma cases undergo treatment at the NCO. The NCO also provides radiation therapy. Both centers are located in the capital city of Yerevan and are publicly owned. The Yeolyan Center comprises several departments, including outpatient and inpatient adult hematology departments, pediatric cancer and blood disorders center, intensive care unit, stem cell transplantation department, department of surgery, blood bank, hemophilia and thrombosis center, pediatric palliative clinic, diagnostic laboratories, and psychological services. Within the Yeolyan Center, a team of 22 hematologists specializes in diagnosing, treating, and managing both malignant and benign hematologic disorders. Additionally, 16 pediatric oncologists provide medical care for patients with these hematologic conditions as well as solid tumors.

Over the last decade, several professional hematological and hematological/oncological associations have been established in Armenia. These organizations play an active role in organizing scientific meetings and collaborating with similar organizations from around the world, all aiming to foster the growth of specialists in this field in Armenia and promote scientific inquiry.

Diagnostic services

Yeolyan Center is the main referral center for the verification of blood disorders in the country. It has well-equipped morphological, biochemical, hemostasis, histological, microbiology, serology and immune hematology, molecular biology, and cytogenetics laboratories. Immunophenotyping and genetic analyses involving FISH, RT-PCR, and karyotyping are performed here[9]. We currently operate the only laboratory in Armenia offering immunophenotyping for leukemia diagnosis using an 8-color flow cytometer from Beckman Coulter. This capability allows us to provide detailed and accurate analyses essential for diagnosing and treating hematological malignancies. Given our specialized position, we prioritize a swift turnaround time for all samples, typically aiming to deliver results within 24 hours. This ensures that patients and clinicians receive timely and actionable information. Performing these critical tests in-house not only accelerates the diagnostic process but also enhances quality control and result reliability. In the realm of genetic and molecular diagnostics, several obstacles persist, including the high cost of advanced testing, limited availability of cutting-edge equipment, and the lack of widespread insurance coverage for these services. It is important to acknowledge that the scope of identified genetic abnormalities (such as FLT3, IDH, NPM1, etc.) is currently limited, impacting the ability to provide a comprehensive prognosis, risk stratification, and treatment decisions. However, ongoing initiatives aim to address these challenges. Efforts are being made to upgrade laboratory facilities and expand access to modern diagnostic technologies, such as next-generation sequencing and advanced molecular assays. Consequently, there is a growing push for both government and private sector involvement to implement and subsidize these tests, making them more affordable for patients.

Improving molecular and genetic testing capabilities in Armenia has the potential to enhance patient outcomes. By enabling earlier and more precise diagnoses, these advancements allow for treatments to be more effectively tailored to individual patients, which can lead to more effective care and potentially better survival rates.

The Stem Cells Laboratory manages the processing and cryopreservation of stem cells from peripheral blood, bone marrow, and cord blood to ensure viability for transplantation. The laboratory has five cryostores, each capable of storing up to 100 bags. Samples undergo rigorous testing before processing, adhering to Good Manufacturing Practice standards in dedicated A and B-class laboratories according to GMP cleanroom quality standards. The laboratory features a biobank capable of preserving stem cells with uninterrupted biological activity over extended periods[9]. Histology and immunohistochemistry for lymphomas are also available at several private and public labs. Genetic analysis is also available at a few labs outside of Yeolyan Center. Radiology services are quite well developed in the country, and almost every large hospital has a CT, and there are a good number of MRIs as well in the country. Two PET-CTs are currently operating in Yerevan – a public one and a private one.

Treatment and outcome of hematologic neoplasms in Armenia

Acute leukemias

Acute leukemias (AL) are characterized by the clonal proliferation of malignant blast cells in the bone marrow along with impaired normal hematopoiesis. The two major subtypes of AL include acute myelogenous leukemia (AML) and acute lymphoblastic leukemia (ALL)[10,11].

In Armenia, the age-adjusted incidence rate of AL from 2012 to 2018 was 1.9 and 1.5 per 100 000 population for AML and ALL, respectively. Rates are similar to those in low- or middle-income countries, however, they are lower compared to those in developed countries[12]. For instance, in the US, the annual rate of new cases of AML and ALL was 4.1 and 1.8 per 100 000 people, respectively[13,14]. The risk stratification for AML is based on European LeukemiaNet (ELN) classification[15] with some limitations. In ALL, risk is assessed using age, white blood cell count, cytogenetics, molecular markers, minimal residual disease (MRD) levels, and response to initial therapy. In Armenia, the main induction chemotherapy regimen for newly diagnosed AML patients is "7+3"[16]. Consolidation chemotherapy is mainly performed with high-dose cytarabine (HiDAC), although some patients may receive consolidation with "7+3" followed by maintenance therapy with cytarabine and 6-mercaptopurine[17]. For patients who are ineligible for intensive chemotherapy, lower-intensity therapies include hypomethylating agents (usually azacytidine), low-dose cytarabine (LDAC) +/- venetoclax[18,19,20].

Therapy for acute promyelocytic leukemia typically involves regimens that incorporate all-trans-retinoic acid (ATRA) and intravenous arsenic trioxide (ATO)[21], and additional anthracyclines for high-risk patients[22].

In Armenia, the primary treatment regimen for adult patients with ALL under 55 years old was the GMALL 07/2003 protocol, replaced by GMALL 2017 version 3 in 2021[23,24]. Patients aged 55 years and older are treated with the GMALL 2017 protocol for patients over 55 years of age or the GMALL 1989 protocol[25]. Patients with Philadelphia chromosome-positive ALL (Ph+ ALL) are treated with the GMALL 09/2017 protocol for Ph+ ALL, which includes the BCR-ABL1 tyrosine kinase inhibitor (TKI) imatinib.

Unfavorable-risk acute leukemias and relapsed/refractory (RR) disease patients are being considered for undergoing allogeneic hematopoietic cell transplantation (HCT) abroad, with the associated costs covered by the patients themselves. In August 2023, the first allogeneic HCT in Armenia for a child with leukemia was performed, and this treatment modality will gradually be available to other patients, eliminating the need to go abroad for these procedures.

Myelodysplastic syndromes

Myelodysplastic syndromes (MDS), a heterogeneous group of hematologic neoplasms, have an annual incidence of approximately 4 per 100 000 people, according to the US SEER database[26]. Based on unpublished data of the retrospective analysis covering 2008-2020, the incidence of MDS in Armenia is around 10 times lower compared to the US, standing at 0.35 cases per 100 000 population, indicating a significant epidemiological deviation from international data, probably due to the population number. The median age at diagnosis of individuals with MDS in Armenia was

62 years (age range, 19-84). The male-to-female ratio revealed a slight male predominance, with a ratio of 1.2 males for every female, comparable with US data[27]. The distribution of MDS subtypes within the Armenian cohort reveals that MDS with multilineage dysplasia (MDS-MLD), MDS with single lineage dysplasia (MDS-SLD), and MDS with excess blasts type 2 (MDS-EB2) were the most prevalent forms, comprising 29.24%, 27.3%, and 12.3% of cases, respectively. In Armenia, the distribution across risk categories based on the IPSS-R was as follows: very low (41%), low (25%), intermediate (16%), high (9%), and very high (9%). One comparative analysis of MDS subtype distribution revealed approximately 17% very low, 40% low, 20% intermediate, 12% high, and 11% very high-risk MDS in Western countries. In contrast, Asian countries had a higher prevalence of high-risk subtypes, with the distribution being approximately 4% very low risk, 32% low risk, 29% intermediate risk, 18% high risk, and 17% very high risk[28].

The predominant treatment approach is supportive care, including blood transfusion, with 41.5% of patients undergoing this intervention, highlighting the importance of consistent iron chelation therapy to prevent associated complications, although chelation is not always performed consistently. Depending on the availability, treatment with azacytidine (7.5%), erythropoiesis-stimulating agents (6.6%), lenalidomide (3%), and allogeneic HCT (1.8%) were performed in some patients. A cytogenetic analysis was initiated in 2021, enabling us to perform risk stratification using IPSS-R and IPSS. Before this, routine cytogenetic testing was not conducted, and survival calculations for risk groups were not performed. In the Armenian MDS cohort, the median progression-free survival was 57 months, while the median overall survival (OS) reached 73.3 months. Globally, patients with lower-risk MDS have a median OS of 3-10 years, while patients with higher-risk disease have a median survival of less than 3 years[29].

Myeloproliferative neoplasms

Chronic myeloid leukemia (CML) is a myeloproliferative disorder that can be cured with TKIs with a 5-year OS rate of over 90% [30]. The incidence of CML in Armenia from 2014 to 2018 per 100 000 people was 0.7, 0.6, 0.8, 0.4, and 0.9, for each respective year. These rates resemble those observed in Europe and indicate an upward trend[31]. Treatment of CML in Armenia improved significantly with TKIs. Since 2003, frontline imatinib therapy has become a standard for all CML patients. Subsequently, in 2017, ponatinib and nilotinib were also available[30]. In 2014-2018, a total of 102 patients were diagnosed with CML (including 4 pediatric patients). The sex distribution exhibited a male-to-female ratio of 1.17:1. Initially, 85% of patients were diagnosed in the chronic phase, while 9% were classified as the accelerated phase, and 6% as blast crisis. Patients categorized as high risk amounted to 15.7% based on Eutos, 28.4% according to Sokal, and 23.5% as indicated by the Euro risk scores. By the end of the study period, more than 75% of CML patients achieved complete remission, approaching rates set by developed countries[31]. The 5-year OS rate for the period 2010-2015 stood at 92% which aligns with global statistics[30]. Data on disease-free survival for CML is not yet available, and investigations are ongoing. There are currently 296 CML patients on active treatment, of whom 226 are treated with imatinib, 45 with nilotinib, and 25 with ponatinib. Starting from January 2021, regular molecular monitoring and monitoring-based treatment have been conducted in Armenia, which opens the possibility of implementing in October 2022 a pilot program of treatment-free remission with regular molecular monitoring, currently including 3 patients.

Primary myelofibrosis (PMF), polycythemia vera (PV), and essential thrombocythemia (ET) are the main Philadelphia chromosome-negative myeloproliferative neoplasms (MPN), which is a heterogeneous group of clonal blood disorders frequently accompanied by mutations in JAK2, CALR, or MPL, although not consistently[32]. A retrospective study examining the pattern of MPN in Armenia in the 2005-2019 period reported the mean yearly incidence of MPN of 1.84 cases per 100 000 people, comprising 2.10 for males and 1.64 for females [33]. Incidence rates of patients with Ph-negative MPNs are presented in Figure 1[32]. The PMF had the highest annual average incidence rate at 1.09 per 100 000 population in 2018, while PV recorded a rate of 0.89 in 2016. In contrast, ET had the lowest incidence rate, standing at 0.7 per 100 000 population in 2016[32]. In comparison, the overall incidence rates in the US were 1.55 for ET, 1.57 for PV, and 0.44 per 100 000 person-years for PMF, with the rising incidence of ET[34]. Another retrospective study examined data from PMF patients from 2010 to 2020 in Armenia. The median age of patients was 60 years (range, 28-88), and 43% were female. Among 112 patients, only a small subset of patients had their JAK2 or MPL mutations, along with other clonal indicators, evaluated, 11 and 2 patients, respectively. CALR was not examined in any

patient. Furthermore, 12 patients were evaluated for BCR/ABL and showed a negative result. Over 74% of patients were prescribed hydroxycarbamide, 5.3% underwent treatment with ruxolitinib, and 6.3% with interferon-alpha, the remaining patients were under the follow-up[35]. Additionally, the study reported a 5-year OS of 40%, and a median survival of patients of 44 months (95% CI: 30-58 months)[35]. While the median OS in the US was 3.6 years[34].

A nationwide study on ET conducted in Armenia included individuals diagnosed with ET between 2003 and 2019. The median age at diagnosis was 52 years, and 68% of those diagnosed were female[36]. Notably, in the US the median age at PMF diagnosis was between 50 and 60 years, and there was no significant sex predominance[37]. Bone marrow biopsy confirmation for ET was available for over 77% of patients at the time of diagnosis. Genetic testing for the JAK2 V617F mutation was conducted on 13 patients (17%) during the study period. Regarding initial treatments, hydroxyurea was the primary choice (92%), followed by low-dose aspirin (6.4%) and interferon-alpha (1.6%) for a subset of patients. Analysis of outcomes revealed a 5-year OS of 87% for the studied group, which decreased to 70% by the 10-year mark (36). For comparison, data from 7 international centers showed that the 10-year survival rate was 89%[38]. Data on PV is currently being collected, will be documented, and reported. The main treatment options include hydroxyurea, ruxolitinib, and phlebotomy.

Chronic lymphocytic leukemia

Chronic lymphocytic leukemia (CLL) stands as the most prevalent form of leukemia among adults. The integration of diverse targeted medications significantly improved the outcomes for CLL patients in the developed world[39]. The annual incidence of CLL in Armenia, calculated for the period 2020-2022, was 2.1 cases per 100 000 people. This is two times lower than the rate in the US, where the incidence is 4.6 per 100 000 population [40]. This substantial difference could be attributed to lower rates of insurance-covered preventive screenings, reduced clinic visits by patients with mild or no obvious clinical symptoms, and a lower average life expectancy of 75.55 years in 2023, compared to 79.11 in the US[41,42]. Upon conducting a retrospective study of all deceased CLL patients in Armenia spanning from 2016 to 2021, it was revealed that the median age of disease onset was 65 years, with a higher occurrence in males (with a male/female ratio of 1.4:1). The most prevalent stage at diagnosis, according to the Rai-Binet classification, was stage IIB[43]. Within the examined population, 69% of patients underwent treatment for CLL and the most used regimens were bendamustine + rituximab[44], fludarabine + cyclophosphamide, or fludarabine + cyclophosphamide + rituximab[45]. Ongoing research aims to provide insights into the outcomes and long-term effects in patients diagnosed with CLL.

Multiple Myeloma

Multiple myeloma (MM) stands as the second most prevalent form of blood cancer in adults, resulting in approximately 117 000 fatalities each year worldwide[46]. Notably, modern progress in diagnostic methodologies and therapeutic alternatives for MM has revolutionized our understanding of the ailment, resulting in heightened survival rates and enhanced well-being among affected individuals[47]. Nonetheless, the advancement in management and comprehensive care in low- or middle-income countries lags, resulting in unfavorable patient outcomes[48]. A retrospective cohort study revealed that between 2006 and 2018 in Ar-

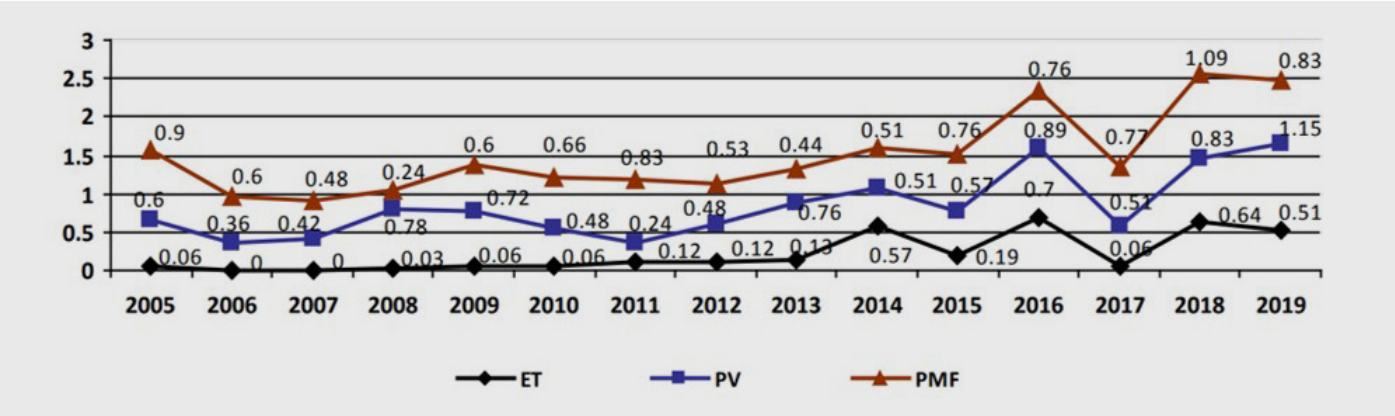

Figure 1. Incidence rates of patients with MPN depending on the type of disease during 2005-2019 (per 100 000 inhabitants) [33]

menia, the yearly average incidence rate for MM was 1.2 per 100 000 people. Notably, a considerable rise was evident in 2018 when compared to 2006, with rates of 1.9 and 0.7 per 100 000 people, respectively. No discernible sex variations were found in the overall incidence of MM throughout the study period[49]. Globally, the incidence rate of MM is approximately 2 cases per 100 000 individuals, although this figure varies significantly. The highest rates are observed in highly developed countries like the US and Western Europe (≥4 per 100 000 population), probably due to greater awareness of the disease and more available diagnostic techniques[50]. Like other developing regions, Armenia experiences remarkably lower survival rates among MM patients compared to countries with more advanced economies mainly due to the availability of new targeted therapies in developed countries. A recent study conducted in Armenia revealed that the 1-year OS rates for MM patients diagnosed from 2008 to 2016 were 64.1% to 68.1%, and the 5-year OS was 17.6% to 18.5%[49]. In comparison, 5-year relative survival in the US was 59.8%[51]. Several crucial tools are unavailable in Armenia, primarily due to economic constraints. These tools encompass the FISH panel for MM, metaphase cytogenetics, gene expression profiling, and plasma cell labeling index[48].

At the Yeolyan Center, the preference leans towards utilizing the VCD regimen (bortezomib, cyclophosphamide and dexamethasone)[52] more frequently when compared to the VRD regimen (bortezomib, lenalidomide and dexamethasone)[53], mainly due to the relatively elevated cost associated with lenalidomide. Among the less commonly employed regimens, we give preference to the lenalidomide and dexamethasone (Rd) protocol[54], followed by cyclophosphamide and prednisolone (CP)[55], bortezomib in conjunction with doxorubicin and dexamethasone (PAD)[56], bortezomib combined with thalidomide and dexamethasone (VTD)[57], or the vincristine, carmustine, melphalan, cyclophosphamide, and prednisone (VBMCP) regimen[58], listed in order of frequency[48]. Patients under the age of 65 who meet the eligibility criteria undergo autologous stem cell transplantation (ASCT). Novel agents such as carfilzomib, daratumumab, and pomalidomide are typically reserved for second-line treatment strategies and patients rarely can afford them.

Additionally, the use of older regimens such as melphalan and prednisolone (MP)[59], CP or VBMCP is still maintained, as their treatment costs are comparatively lower. Among the less frequently employed approaches, thalidomide and dexamethasone (TD)[60] and the combination of cyclophosphamide, lenalidomide and dexamethasone (CRD) are also considered[61].

Non-Hodgkin lymphoma

A concerning rise in the incidence of hematological malignancies has notably been exhibited in the escalating prevalence of non-Hodgkin lymphoma (NHL). As the most prevalent hematological malignancy worldwide, NHL accounts for nearly 3% of cancer diagnoses and fatalities[62]. A retrospective analysis of the amassed data revealed an average annual incidence of 4.34 NHL cases per 100 000 individuals during the 2017-2021 period in Armenia[62]. Comparative assessment with prior studies (1998-2004 and 1966-1971) unveiled a surge in NHL incidence rates, with a 1.5-fold and 4-fold increase, respectively. Notably, a substantial upswing occurred in 2019 compared to 2017, with rates of 5.9 and 3.3 NHL cases per 100 000 individuals, respectively. Age-standardized risk assessment demonstrated NHL rates of 4.8 among males and 3.9 among females. In both sexes, the elevated incidence was prominent in the age group of 55 years and older. This study illuminated a substantial escalation in NHL incidence rates across the examined period[62]. Ongoing endeavors are directed toward dissecting the statistics about specific lymphoma subtypes. Preliminary findings indicate that in Armenia diffuse large B-cell lymphoma (DLBCL), the most common type of aggressive NHL, accounts for 30% of cases similar to international data, while unclassified lymphomas constitute 20%-25%[62,63].

In Armenia, the treatment landscape for aggressive NHLs primarily revolves around the widely used R-CHOP protocol (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone)[64]. Indolent forms of NHL that require treatment have several options available. The primary treatment approach often involves chemotherapy with or without rituximab, utilizing regimens like R-CVP (cyclophosphamide, prednisolone, rituximab and vincristine)[65], CVP (cyclophosphamide, prednisolone and vincristine)[66], BR (bendamustine and rituximab), R-CHOP, and rituximab monotherapy. Radiotherapy as first-line treatment is not usually performed. In recent years, cladribine has become the standard treatment for hairy cell leukemia, with pentostatin not being accessible. The utilization of rituximab represents the primary immunotherapy option for many types of NHL treatment in Armenia. Rituximab is accessible in Armenia, albeit with

certain difficulties associated with the availability of the drug in only a few pharmacies in the country, and sometimes with the need for pre-ordering. Notably, other immunotherapy agents are not officially registered in the country. This absence of formal registration presents obstacles in terms of insurance coverage, resulting in the requirement for patients to acquire these treatments out-of-pocket. This financial aspect can pose significant challenges for patients, limiting their access to these potentially life-saving therapies.

Currently, data on the survival rates of NHLs is unavailable. Ongoing research is essential to provide insights into the prognosis and treatment efficacy for patients with this condition.

Hodgkin lymphoma

Hodgkin lymphoma (HL) is one of the most treatable malignant diseases, boasting a 5-year survival rate of over 80%[67]. The annual age-adjusted incidence rate in Armenia over 15 years (2000-2014) was 2.3 cases per 100 000 individuals[68], which closely matches the corresponding US data of 2.5 cases per 100 000[69].

Classical Hodgkin lymphoma (cHL) constitutes 95% of all HL cases[70]. In Armenia, between 2015 and 2020, a total of 212 patients were diagnosed with cHL, according to data recently presented at the Society of Hematologic Oncology 2023 Annual Meeting. The mean age of those affected is 45 years, with a range spanning from 20 to 83 years. There is a slightly higher male-to-female ratio of 1.09:1. Histological subtypes of cHL were distributed as follows: nodular sclerosis accounts for 54.8%, mixed cellularity for 35.3%, rich in lymphocytes for 8.49%, and depleted in lymphocytes for 1.41%. When newly diagnosed, 56% of patients were presented with advanced disease. The 5-year OS is 91%, comparable to that of the developed world[69]. Approximately 67% of patients underwent treatment with the ABVD protocol (doxorubicin, bleomycin, vinblastine and dacarbazine)[71], while the remaining 33% received treatment with the escalated BEACOPP protocol (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone)[72].

In June 2023 at the Yeolyan Center, the Immune Oncology Research Institute, initiated a phase 2 investigator-sponsored clinical trial (ClinicalTrials.gov: NCT05891821) to evaluate the safety and efficacy of single-agent balstilimab (PD-1 inhibitor) in patients with RR cHL or primary mediastinal B-cell lymphoma[73].

Radiation therapy

Specialized radiotherapy services for hematological patients are available in two institutions in Yerevan and both are located at the NCO. The main provider of radiation oncology services in the country is the NCO, which covers more than 80% of cancer radiotherapy services in Armenia. The treatment costs for all patients in this public center are completely covered through a state-funded program launched in 2019.

The External Beam Radiotherapy (EBRT) Department of the NCO operates two EBRT complexes: one telecobalt device (Terabalt, 2006, Czech Republic) and one single energy (6MV) linear accelerator with multileaf collimators. The department is currently staffed with 7 radiation oncologists, 5 medical physicists, and 7 radiotherapy technologists.

Table 1. Radiotherapy utilization rates for hematological malignancies in Armenia, 2020

Type of malignancy	Number of primary cases in 2020	Should have been irradiated according to internationally accepted RTU levels (Optimal RTU, %)	Received radiotherapy in 2020 (Actual RTU, %)	Absolute difference
Leukemia	183	7 (4%)	6 (3%)	-1
Myeloma and plasmacytoma	57	26 (45%)	3 (5%)	-23
Lymphoma	181	132 (73%)	49 (27%)	-83

Abbreviation: RTU, radiotherapy utilization rate

Although cobalt-based 2D conventional radiotherapy is still in use in some situations (e.g., palliation, prophylactic cranial irradiation, etc.) because of a scarcity of technical resources, most patients with hematological malignancies are treated with linac-based 3D conformal radiotherapy. Involved site radiation therapy is the main option for lymphoma patients with CT-based computerized 3D treatment planning and the use of PET-CT image registration when available. Multi-disciplinary team discussions for all, including hematological patients before decision-making for radiotherapy are mandatory at NCO. However, in many cases, patients are seen by radiation oncologists only after completion of chemotherapy or other treatments, and radiation oncologists often are not involved in the initial decision-making process.

There is also a private institution operating a dual-energy linear accelerator staffed with 3 radiation oncologists where some patients are treated on a pay-per-service basis.

Hence, with 3 EBRT units in the country with about 3 million population, against the internationally recommended 10-12, lack of local training resources and infrastructures for core radiation oncology specialists and gaps in staffing, radiotherapy is the "bottleneck" in the continuum of comprehensive cancer services, which also influences the management of the hematological oncology patients[74]. In addition, such modalities as image-guided radiotherapy, volumetric arc therapy, stereotactic radiotherapy, total body irradiation, and radioimmunotherapy currently are not available in Armenia.

This, along with the high fragmentation of cancer care services, the lack of national standards and guidelines in the field, and an ineffective communication culture between specialists, largely explains the low utilization rates of radiotherapy in the treatment of hematological malignancies in Armenia (Table 1), particularly for lymphomas and myeloma.

Considering the current and growing needs for modern radiotherapy services, in 2021 NCO initiated a 3-year radiation oncology capacity building program with the construction of a new technological building and acquisition of two new high-energy linear accelerators. The implementation of the program will allow for fundamentally improving the situation with radiotherapy services in the country and cover the needs of the country's population in state-of-art radiotherapy modalities.

Stem cell transplantation

Since its inception in 2017, the Armenian Bone Marrow Transplant program has achieved significant milestones. Beginning with ASCT for multiple myeloma in 2 patients in April 2017, the program has completed a total of 108 ASCTs as of August 9, 2023. Of these, 85 procedures were conducted in adults, spanning ages 19 to 67, while 23 were performed in pediatric patients aged 2 to 17.

For adult patients, the diagnostic spectrum encompasses a range of conditions, including RR HL and various subtypes of RR NHL such as DLBCL, follicular lymphoma, mantle cell lymphoma, primary central nervous system lymphoma, peripheral T-cell lymphoma, and MM. Meanwhile, pediatric patients underwent ASCT for diagnoses including RR HL, medulloblastoma, and Ewing's sarcoma, as well as high-risk neuroblastoma.

Looking ahead, the program plans to expand by implementing allogeneic stem cell transplants for patients with hematologic malignancies in the near future. Notably, in July 2021, the Yeolyan Center marked a milestone by performing its first allogeneic hematopoietic stem cell transplant (HCT) on a pediatric patient with sickle cell disease[9]. In August 2023 the center conducted its first allogeneic HCT on a pediatric leukemia patient. The transplant department has seven beds. The wards are equipped with a high-efficiency particulate air (HEPA) filtration system, laminar air flow and positive pressure.

Palliative care

Until 2021, Armenia lacked facilities to provide palliative care for pediatric patients. Specifically, children with serious conditions would often pass away either at home or in intensive care units, without receiving adequate pain relief or symptom management, and frequently being separated from their families. With support from the City of Smile charity, Armenia's first Pediatric Palliative Care Clinic was established at the Yeolyan Center in September 2021. The clinic is designed for children up to 18 years old with malignant diseases. It can accommodate up to five patients and is fully outfitted with fully equipped with amenities and essential medical equipment. The City of Smile Charitable Foundation ensures a steady supply of medications and provides four daily meals. Since the clinic's establishment, 29 children have received treatment.

Children and their families receive support from a psychosocial team, including bereavement support groups. If the parents and/or the child choose to return home, we coordinate with the primary physician and maintain ongoing communication with the family to ensure effective care and continued support. Additionally, the palliative care team is actively involved in the care and symptom management of children undergoing treatment in the pediatric oncology and hematology departments as needed, facilitating a smoother transition to the palliative clinic. This year, pilot mobile palliative care services for children under 18 will be launched in Yerevan and four nearby regions. The program, funded by the Ministry of Health, will also include children who require palliative care for conditions other than cancer. In 2022, a large 30-bed well-equipped, modern adult palliative care clinic was established at NCO, which provides inpatient and outpatient palliative care services for oncology patients, including those with hematologic malignancies. Few specialists also provide outpatient palliative care services throughout the country. Currently, pain control and supportive care service is in the process of establishment at the Yeolyan Center. There are several small, private hospices also operating in Armenia, where patients mostly could receive end-of-life care.

Future perspectives

In addition to the above-mentioned initiatives, there are currently several efforts underway to enhance the field of hematologic oncology in Armenia. Nationwide electronic prospective registries (acute leukemias, CLL, MM) are being implemented to enable a more accurate and comprehensive situation analysis. Registries for Ph-negative MPNs and MDS are already running. The full integration of e-health systems at the Yeolyan Center is planned to be completed within the next 2-3 years.

With the establishment of disease-specific working groups and fostering collaboration among multidisciplinary teams, Armenia can effectively implement and adapt diagnostic and treatment approaches in hematologic oncology, improving patient care and outcomes. Experienced professionals are assigned to lead each working group, arranging regular meetings to review progress, share insights, conduct a thorough review of current scientific literature for evidence-based diagnostic and treatment strategies, and adapt standardized guidelines as needed. One of the main challenges is the availability and accessibility of medications in the country. While for the essential medications, the main issue is the official registration of certain medications in Armenia and the assurance of their quality, for the novel therapies the main obstacle is the cost of those medications. In the coming years, Armenia is planning to implement nationwide compulsory medical insurance, which hopefully will alleviate the current realities. Key drugs such as TKIs of three generations are funded by The Max Foundation. Recently, second-generation Bruton's tyrosine kinase (BTK) inhibitors for CLL patients have also become accessible due to the Foundation's support. In addition, as part of this collaboration, zanubrutinib, a new and promising drug, has become available to our patients. Several initiatives are ongoing for novel medications to bring clinical trials to the country and make investigational therapies accessible for Armenian patients.

The implementation of allogeneic HCT and CAR-T cell therapy in Armenia is emerging, offering potentially curative options for our patients. We are developing and strengthening partnerships with international centers and foundations, including Cure2Children Foundation and Moffitt Cancer Center. These collaborations are vital for knowledge exchange, training, and research, and will help to establish and enhance these advanced therapies in Armenia.

Furthermore, there is an increasing emphasis each year on the advancement of scientific research in Armenia. This emphasis is reflected in the heightened engagement of professionals in conducting and participating in clinical trials, attending international scientific events, and fostering the promising careers of young specialists. These initiatives collectively contribute to the strengthening of Armenia's presence and influence within the global scientific community, while also fostering the development of the nation's healthcare sector and the next generation of scientific leaders. Armenian hematologists-oncologists are also striving to make contributions to global medical and scientific endeavors. In this context, it is worth mentioning the commencement of the blastic plasmacytoid dendritic cell neoplasm (BPDCN) international registry in 2022 (ClinicalTrials.gov: NCT05430971), initiated by the Immune Oncology Research Institute, which is the only similar initiative globally and currently 17 centers from 14 countries are already part of it[75]. Given the absence of a consensus on the optimal treatment for BPDCN and its rarity, international collaboration is crucial. This collaboration aims to collect data on BPDCN patients, establish a comprehensive patient database, investigate the

disease's characteristics, evaluate prognostic factors and outcomes, and develop prospective treatment recommendations.

Our center has recently joined a Phase 1b, multicenter, open-label clinical trial (ClinicalTrials.gov: NCT04953897) that evaluates the pharmacokinetics, safety, and tolerability of multiple doses of oral decitabine and cedazuridine in cancer patients with severe renal impairment as well as those with normal renal function serving as matched control subjects. This study enrolls adult patients with AML, MDS, or solid tumors who are eligible for treatment with these medications[76].

To further advance our understanding and management of hematologic malignancies, we propose several key areas for future research. One of them is the clinical significance of the JAK2 (V617F) allele burden in Ph-negative MPNs. Understanding its potential influence on disease course and management could provide critical insights into optimizing treatment protocols and improving patient stratification.

CONCLUSION

Considerable progress has been observed in the field of hematological oncology in Armenia in recent years, however, many challenges still need to be addressed. Referring to the gaps and limitations, some diagnostic tools are not available yet or are not routinely performed in the country due to the lack of financial coverage. The lack of genetic and molecular data hampers our ability to fully understand the pathophysiology of diseases within the Armenian population and restricts personalized treatment approaches, making this a limitation of this study. The disparities in incidences of different types of hematologic malignancies are likely attributed to disease awareness and accessibility to diagnostic techniques. Additionally, the availability of advanced treatment options remains limited. The scarcity of treatment options underscores the need for increased efforts to expand the range of accessible medications for patients with hematologic malignancies in the country. Despite these challenges, the medical community in Armenia remains committed to providing the best possible care for the patients. Efforts are underway to address these issues by advocating for the registration of therapeutic agents and exploring avenues for funding assistance. As the healthcare landscape evolves, we hope that increased accessibility and support will improve the treatment options, and outcomes of individuals facing hematologic malignancies in Armenia.

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Abbreviation	Explanation	Abbreviation	Explanation
ABVD	Doxorubicin, bleomycin, vinblastine and dacarbazine	**LDAC**	Low-dose cytarabine
AL	Acute leukemias	**LMICs**	Low or middle-income countries
ALL	Acute lymphoblastic leukemia	**MDS**	Myelodysplastic syndromes
AML	Acute myelogenous leukemia	**MDS-EB2**	Myelodysplastic syndromes with excess blasts type 2
ATRA	All-trans-retinoic acid	**MDS-MLD**	Myelodysplastic syndromes with multilineage dysplasia
ATO	Arsenic trioxide	**MDS-SLD**	Myelodysplastic syndromes with single lineage dysplasia
ASCT	Autologous stem cell transplantation	**MM**	Multiple myeloma
BEACOPP	Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone	**MP**	Melphalan and prednisolone
BPDCN	Blastic plasmacytoid dendritic cell neoplasm	**MPN**	Myeloproliferative neoplasms
BR	Bendamustine and rituximab	**MRD**	Minimal residual disease
BTK	Bruton's tyrosine kinase	**MRI**	Magnetic resonance imaging
CML	Chronic myeloid leukemia	**NHL**	Non-Hodgkin lymphoma
CI	Confidence interval	**NCO**	National Center of Oncology
CLL	Chronic lymphocytic leukemia	**OS**	Overall survival
CT	Computed tomography	**PAD**	Bortezomib, doxorubicin and dexamethasone
CRD	Cyclophosphamide, lenalidomide and dexamethasone	**PET-CT**	Positron emission tomography-computed tomography
CVP	Cyclophosphamide, vincristine and prednisolone	**PMF**	Primary myelofibrosis
DLBCL	Diffuse large B-cell lymphoma	**PV**	Polycythemia vera
EBRT	External beam radiotherapy	**R-CHOP**	Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone
ELN	European LeukemiaNet	**R-CVP**	Rituximab, cyclophosphamide, vincristine and prednisolone
ET	Essential thrombocythemia	**Rd**	Lenalidomide and dexamethasone
FISH	Fluorescence in situ hybridization	**RR**	Relapsed / refractory
GMP	Good Manufacturing Practice	**RT-PCR**	Reverse transcription polymerase chain reaction
HCT	Hematopoietic cell transplantation	**RTU**	Radiotherapy utilization rate
HEPA filtration	High-efficiency particulate air filtration	**SEER**	Surveillance, epidemiology and end results program
HiDAC	High-dose cytarabine	**TD**	Thalidomide and dexamethasone
HL	Hodgkin lymphoma	**TKI**	Tyrosine kinase inhibitor
cHL	Classical Hodgkin lymphoma	**VCD**	Bortezomib, cyclophosphamide and dexamethasone
HIV/AIDS	Human immunodeficiency virus / acquired immunodeficiency syndrome	**VRD**	Bortezomib, lenalidomide and dexamethasone
IPSS	International Prognostic Scoring System	**VTD**	Bortezomib, thalidomide and dexamethasone
IPSS-R	Revised International Prognostic Scoring System	**VBMCP**	Vincristine, carmustine, melphalan, cyclophosphamide and prednisone