ISSN No:-2456-2165

# A Review on the Role of C Kit /SCF System in Hematological Malignancies

Darshana Kottahachchi, Chamila Nandasena, Sachini Gallage,
Department of Medical Laboratory Sciences
Faculty of Allied Health Sciences
General Sir John Kotelawala Defence University
Sri Lanka

Inoka C. Perera
Department of Zoology and Environmental Sciences
Faculty of Science
University of Colombo
Sri Lanka

Darshan De Silva
KDU care
General Sir John Kotelawala Defence University
Sri Lanka

Sasikala Suresh
Department of Hematology
Apeksha Hospital Maharagama
Sri Lanka

**Abstract:- Hematological cancers are a major cause for the growing of mortality rate in patients worldwide. Myeloid and lymphoid malignancies are the main subtypes of blood cancers, and the distribution of them is different according to the geographical details. However, a considerable global population is affected by these cancers and it is essential to find some blood indicators specific for the subtypes of myeloid and lymphoid cancers. The availability of such blood markers helps to early diagnosis, treatment monitoring and grading of a cancer. Expression of some receptors on normal and diseased blood cells help the purpose as an indicator. Tyrosine protein kinase kit (C Kit) / Ligand-Stem Cell Factor (SCF) systems are responsible for the hematopoietic cell proliferation, cell survival and certain intracellular activities that takes place in the normal condition. C Kit receptor also shows a co expression with similar tyrosine kinase receptors which has same functions. In this review, we study the presence of C Kit (CD 117) on blood cells in hematological cancers to investigate the possibility of using C Kit/SCF systems for novel drug targets for them.**

***Keywords:-*** *C Kit System, SCF, Hematological Cancers, Blood Indicators.*

## I. INTRODUCTION

### *A. What are the hematological malignancies?*

Hematological malignancies are group of clinically and biologically heterogeneous cancers that affect the blood, bone marrow (BM) and lymphatic system. The three main clinical presentations of HM include Leukemia, lymphoma, and multiple myeloma [01,02]. In view of clinical heterogeneity, affected individuals need proper treatments and therapeutic care. Comparably, biologically heterogeneous disease confines those individuals where different molecular pathologies give rise to distinct disease characteristics, i.e. Molecular level changes, molecular mediated resistance to treatments and abnormal biomarker expression [02].

Bone marrow is the place where normal hematopoietic stem cells differentiate into cells of the myeloid or lymphoid lineage. In the process of myelopoiesis granulocytes, monocytes, mast cells, erythrocytes and thrombocytes differentiate from myeloid precursor cells. Likewise, in the lymphocytopoiesis T cells, B cells, Natural Killer (NK) cells and plasma cells are produced by the lymphoid precursors. In majority of the HM, bone marrow is the primary site where the tumor begins and confines with peripheral blood and lymphoid organs; spleen and lymph nodes [01].

According to The World Health Organization (WHO) classification of hematological neoplasms, two main categories are determined based on affected lineages as myeloid and lymphoid neoplasms. Further each cell lineage account for variable diseases [02, 03]. Within each category, diseases are defined according to specific characteristics of cell morphology, immunophenotype, genetic features, and clinical presentations [03]. According to 2017 statistics reported in the United States, among all cancers approximately 10.2% was recorded as hematological malignancies [01, 04].

### *B. Myeloid Cancers*

Myeloid malignancies are clonal diseases of hematopoietic stem or progenitor cells that can be present in the bone marrow and peripheral blood [05]. According to French- American-British (FAB) classification, three types of myeloid cancers are identified: acute myeloid leukemias, myelodysplastic syndromes, and myeloproliferative disorders based on the characteristics of the blast cell count, lineage involvement, and the differentiation ability of the neoplastic cells which are diagnosed by morphologic, cytochemical, and immunophenotypic methods [03].

In the clinical set up both acute and chronic stages of Myeloid malignancies can be found. Around 80% of Acute myeloid leukemia (AML) can lately transform into a chronic stage which are diagnosed as myeloproliferative neoplasms (MPN), myelodysplastic syndromes (MDS) and chronic myelomonocytic leukemia (CMML). Further based on

cytogenetics and phenotypic characteristics, AMLs can be differentiated into AML with favorable, intermediate, and unfavorable. MPNs are a collective of four different cancers such as chronic myeloid leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF) [06,07].

*C. Epidemiological survey on myeloid cancers*

Acute myeloid leukemia (AML) is the most common acute leukemia in adults. It accounts for around 80 percent of cases in adults and in children aged below 10 years AML results for less than 10 percent. Prevalence of AML results in about 1.3 per 100,000 under age 65 years and about 12.2 per 100,000 over 65 years. In accordance with age acute myeloid leukemia in the years from 1975–2003 was 3.7 per 100,000 persons [05].

Apart from myeloid malignancies CML is the most abundant hematological cancer in Asia, but its occurrence may be lower than the reported cases in US [08]. Treatment methods for CML in Asia have altered intensely over the past years, and patients can anticipate extended median survival [09]. However, it is rational to assume that the combined age-adjusted incidence rate for all myeloid malignancies in the U.S. is less than 15 per 100,000 individuals, depending on the reported incidence of myeloid malignancies in general. [05].

Individual occurrence rates have not been published for each type of myeloid neoplasm. For 2006-2010, the age-adjusted combination incidence rate for MDSs, MPNs and chronic myelomonocytic leukemia was 7.8 per 100,000 individuals. All other myeloid malignancies are very rare, and their precise incidence is not primarily present. Considerably all other myeloid malignancies are very rare, and their exact incidence is not knowing currently. There is a high predictability of CML occurrence rates of 0.6-2.0 cases per 100,000 populations, according to the SEER database, data extracted from nine separate records of around 26.5 million populations covering almost 10-14 percent of the total. The prevalence of CML rises with age and is more common in men than in women: the male-to-female ratios differ from 1.3 to 1.8 [10].

*D. Lymphoid malignancies*

Lymphoid malignancies are a cluster of cancers deriving from lymphatic system [11, 12,13,14] which has the responsibility to fight with infections and produce body immunity. Lymph nodes, spleen, bone marrow and thymus are included in lymphatic system and in addition to these regions, other organs in the body are capable to be affected by a lymphoid cancer known as lymphoma. The cause of the disease is unknown in some types of lymphomas. Aging, being a male, having a weak immune system and some infections are considered as risk factors for the lymphomas [14,15]. In most cases, genetic mutation can occur in lymphocytes that can trigger rapid multiplying. Therefore, the amount of abnormal, ineffective lymphocytes is increased and accumulate in lymphatic system and other organs causing swelling of organs. Swollen lymph nodes, fever, night sweating, weight loss and tiredness are the common symptoms of lymphoma [14]. Hodgkin lymphoma, Non-Hodgkin lymphoma, skin lymphomas and waldenstrom macroglobulinemia are the major types of lymphomas [12].

According to the recent criteria of world health organization (WHO), lymphoma is categorized into more than 40 sub types [13]. Main two types of lymphoid cancers are Hodgkin lymphoma (HL) and Non-Hodgkin lymphoma (NHL) [16]. NHL is the most abundant type of lymphoma and it is divided into B cell origin and T cell origin since the B cell lymphomas are abundant [17].

*E. Epidemiological survey on lymphoid malignancies*

Lymphoma is a leading cancer type throughout the world, and it has taken more than 3% from all type of cancers worldwide [18]. It was found that the rate of occurring lymphoid malignancies has been increasing by 3% to 4% during past four decades whole over the world [15]. Prevalence of lymphoma demonstrates a conspicuous ecological distribution [18]. Especially NHL is most abundant in industrialized countries than in developing countries [19]. Highest incidence rate of NHL is shown in Israel, Zimbabwe, Canada, Australia, and New Zealand in 2018 [20].

Lymphoma is the 7$^{th}$ leading cancer type in Sri Lanka and lifetime risk is 0.363 as a percentage (per 100 persons). From all cancers occurred in male population in year 2010, 5% were lymphoma and it is 3% for females. Some age groups are prominently affected by lymphoid cancers. Lymphoma is the secondly highest cancer in the 0 – 14years age group of male while it was in sixth place for female. Lymphoid malignancies are the most abundant cancer type in 15- 34 age group of male while it was in fifth place for females in same age group [21].

## II. IMPORTANCE OF BIOMARKERS FOR CANCERS

The modern style of medicine is to detect biomarkers for a particular disease or disease states. A biomarker is a quantifiable indicator that relates to a specific biological or disease state. It is widely being used for an initial finding, categorization and staging of diseases to assign patients for targeted treatments, to monitor treatment response, and to detect disease recurrence. Biomarkers could be detected in the blood, other fluids, tissues and measured serially could provide a real-time assessment of a patient's disease and response to treatment. Therefore, biomarkers specific diseases look likely to become one of the major driving forces in the pharmaceutical research and drug development [22, 23].

## III. INTRODUCTION ON C KIT/SCF SYSTEM

C kit (CD 117) is a transmembrane protein a member of tyrosine kinase family as FLT3 [ 24,25]. This receptor is present on different cells including immature hematopoietic cells, mast cells and melanocytes [26]. It regulates more functions as cell proliferation, differentiation, and natural cell death. Further, this receptor plays a major role in tumor

occurrence, development, migration, and recurrence [27,28]. Stem cell factor (SCF) is the ligand which activates C Kit receptor [25,29,30] and this ligand is available in both membranes bound and soluble forms. SCF can activate itself alone and with other growth factors [31]. After binding to the C kit receptor, receptor-ligand complex mediates more functions especially the early hemopoiesis [27,32].

*A. C kit (CD 117) and myeloid cancers*

Some cancers express the abnormal activation and mutations in the C kit/SCF system [33]. C kit expression was detected in most leukemic cells [34]. Strong CD117 expression was detected in acute promyelocytic leukemia which is a subtype of AML [35,36]. C Kit was expressed in most AML and myelodysplastic syndromes and little number of ALL patients in the study group [37]. Advani (2006) has studied that C kit was expressed on 10% blasts of most AML and relapsed AML cases while the receptor activates cell proliferation and anti-apoptotic activity [38]. The study done by Hans et al. (2002) found some important information on C kit receptor using flowcytometric analysis of 150 AML cases and stated that the receptor CD117 is a specific marker for AML [39].

*B. C Kit (CD 117) and Lymphoma*

It has been suggested that lymphoid and myeloid lineage cells may express C Kit restricted to presence of antigen on lymphoid lineage; Natural Killer cells and T cell precursor cells [34,40]. However, **Ling et al. (2009)** have revealed that the presence of C Kit in higher amount of immature B cells while they get reduced with the cell proliferation [41]. Especially, the interaction between C kit and SCF causes major role in early lymphopoiesis while SCF helps to mature T thymocytes [42]. In addition to that, by sequencing of fifty oncogenes in three cases of primary mediastinal lymphoma, a subtype of diffuse large B cell lymphoma, two cases have expressed the C kit mutation and it was confirmed by Sanger sequencing [43]. It was observed that lymph nodes in Hodgkin lymphoma express the C kit and degenerative large cell lymphoma a type of Non-Hodgkin lymphoma has expressed the receptor in lymph nodes [44,45].

*C. C Kit/SCF system activity with other receptors*

It was mentioned that FLT3 (CD135) and C Kit (CD 117) have a co expression ability [46]. The similarity of FLT3 (CD135) and C Kit (CD 117) is they are members of tyrosine kinase III family and both receptors are in same structure [46,47]. FLT3 and C Kit antigens have shown a co expression on acute myeloid leukemia blasts by flowcytometry; study done in Iran. The results of their study have proved that the expression of CD135 and CD117 are 77.3% and 84.8%. From that expression, 68.2% was co expressed [46]. **Sharawat et al. (2013)** also detected the more than 20% co expression of both CD117 and CD135 on most of the myeloblasts. Only few studies are available to find the co expression of mentioned receptors [47].

## IV. CONCLUSION

It is right time to study the new hemopoietic systems or the systems that synergizes and antagonizes them as it opens eyes to study the abnormal mechanisms leading to new drug targets. In this review an attempt has been made to summarize the role of C Kit/SCF System on hematological malignancies. This information should be of value for better understanding of current trends and future perspectives of research in leukemia and lymphoma.

## ACKNOWLEDGEMENT

We thank General Sir John Kotelawala Defence University for the support provided in all aspects.

## REFERENCES

[1]. A.K Deshantri, A.V Moreira, V. Ecker, S.N Mandhane, R.M Schiffelers, M. Buchner and M.H Fen, “Nanomedicines for the treatment of hematological malignancies,” J. Con. Relese, vol. 10;287, pp.194-215, August 2018.
[2]. E. Bahakeem and T. Qadah, “Current diagnostic methods for hematological malignancies, A mini-review,” Pharmacophore, vol.11, pp. 63-8, 2020.
[3]. N.L. Harris, E.S Jaffe, J. Diebold, G. Flandrin, H.K. Muller-Hermelink, J. Vardiman, T.A. Lister and C.D. Bloomfield, “The World Health Organization classification of hematological malignancies report of the clinical advisory committee meeting, Airlie House, Virginia, November 1997,” Mod. Pathology, vol. 13(2), pp.193-207, February 2000.
[4]. J. Taylor, W. Xiao and O. Abdel-Wahab, “Diagnosis and classification of hematologic malignancies on the basis of genetics,” Blood, vol 27;130(4), pp. 410-23, July 2017.
[5]. D.D. Howard, World Trade Center Health Program Centers for Disease Control and Prevention (CDC) National Institute for Occupational Safety and Health (NIOSH), 2014.
[6]. Murati, M. Brecqueville, R. Devillier, M.J. Mozziconacci, V. Gelsi-Boyer and D. Birnbaum, “Myeloid malignancies: mutations, models and management,” BMC cancer, vol. 12, pp. 1-5, December 2012.
[7]. Shimada, “Hematological malignancies and molecular targeting therapy,” Eur. J. Pharmacology, vol. 5, pp. 862-172641, November 2019.
[8]. L.A. Ries, M.P. Eisner, C.L. Kosary, B.F. Hankey, B.A. Miller, L. Clegg, A. Mariotto, M.P. Fay, E.J. Feuer and B.K. Edwards, “SEER can. Stat. review,1975–2000 Bethesda,” National Cancer Institute, 2003.
[9]. W.Y. Au, P.B. Caguioa, C. Chuah, S.C. Hsu, S. Jootar, D.W. Kim, I.Y. Kweon, W.M. O’Neil, T.K. Saikia and J. Wang, “Chronic myeloid leukemia in Asia,” Inter. J. hematology, vol. 89(1), pp. 14-23, January 2009.

[10]. M. Rohrbacher and J. Hasford, "Epidemiology of chronic myeloid leukaemia (CML)," Best prac res. Clin. Haematology, vol. 1;22(3), pp. 295-302, September 2009.
[11]. E.S. Jaffe, N.L. Harris, H. Stein, et al., editors. "Pathology and genetics of tumours of haematopoietic and lymphoid tissues," Lyon, France, IARC Press, 2001
[12]. American Cancer Society -Types of Lymphoma, available at; https:// www. cancer.org /cancer /lymphoma.html - Accesssed 21.02.2021
[13]. S. H. Swerdlow, E. Campo, N.L. Harris, *et al*., "The diagnosis of NHL is based upon the pathologic evaluation of involved tissue, usually an abdominal mass, extranodal site, or lymph node, interpreted within the clinical context. World Health Organization classification of tumours of haematopoietic and lymphoid tissues," 2018
[14]. Mayo Clinic -Lymphoma , available at: https://www.mayoclinic.org/diseases-conditions / lymphoma / symptoms-causes/syc-20352638 - [Accessed 21.02.2021]
[15]. J. Huh, "Epidemiologic overview of malignant lymphoma," The Kor. J. of hem., *47*(2), 92–104,2012
[16]. E. Campo, S.H. Swerdlow, N.L. Harris, S. Pileri, H. Stein, E.S. Jaffe, "The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications," Blood ,117(19),5019-32, 2011
[17]. Medscape.int, Non-Hodgkin Lymphoma., Available at: https:// emedicine.medscape.com /article/203399-overview. 2021[Accessed- 21.02.2021]
[18]. *CANCERmondial*. Lyon, France, "International Agency for Research on Cancer," Available at; http://www.dep.iarc.fr/ , 2008
[19]. P.I. Boffetta, "Epidemiology of adult Non-Hodgkin lymphoma," *Annals of Onco.*, 22, 2011
[20]. A. Miranda-Filho, M. Piñeros, A. Znaor, *et al*., "Global patterns and trends in the incidence of non-Hodgkin lymphoma," Can. Causes Con., **30,** 489–499, 2019
[21]. The National Cancer Control Programme, Available at: www.nccp.health.gov.lk /index. php/2011-11-25-07-20-55. [Accessed- 21.02.2021]
[22]. P. Workman, E.O. Aboagye, Y.L. Chung, J.R. Griffiths, R. Hart, M.O. Leach, *et al*., "Review: Minimally invasive pharmacokinetices in hypothesis-testing clinical trials of innovative therapies," J Natl. Cancer Inst., 98,580 –598, 2006
[23]. X. Peng, W. Fei, G. Xin, and W. Zhang, "Current Advances in Tumor Proteomics and Candidate Biomarkers for Hepatic Cancer," Expert Review of Prote., 6(5), 551-561,2009
[24]. C.R. Antonescu, "The GIST paradigm: lessons for other kinase-driven cancers," J. Pathol.,223(2), 251-261, 2011
[25]. S.Q. Chen and A.Q. Xiong, "The progress and implication of stem cell factor," Basic Med. Sci. and Clin.,22(5),385-390, 2002
[26]. I. K. McNiece and R. A. Briddell, "Stem cell factor," J. Leukoc. Biol., 58, 14–22, 1995
[27]. J. Liang, Y.L. Wu, B.J. Chen, W. Zhang, Y. Tanaka, and H. Sugiyama, "The C-Kit Receptor-Mediated Signal Transduction and Tumor-Related Diseases," Int. J. Biol. Sci., 9(5),435-443. 2013
[28]. A. L. Smith, F. M. Ellison, J. P. McCoy, and J. Chen, "c-Kit Expression and Stem Cell Factor-Induced Hematopoietic Cell Proliferation Are Up-Regulated in Aged B6D2F1 Mice," *The J. of Gero., Series A*, Volume 60, Issue 4, Pages 448–456, April 2005
[29]. Y. Yarden, W.J. Kuang, T.Yang-Feng. *et al*.," Human proto-oncogene c-kit; a new cell surface receptor tyrosine kinase for an unidentified ligand," EMBO J.,6(11),3341-3351,1987
[30]. G. Frumento, J. Zuo, K. Verma, W. Croft, P. Ramagiri, F.E. Chen, and P. Moss, "CD117 (c-Kit) Is Expressed During $CD8^+$ T Cell Priming and Stratifies Sensitivity to Apoptosis According to Strength of TCR Engagement," Front. Immunol., 10, 468. 2019
[31]. S. Lev, D. Givol, and Y. Yarden, "A specific combination of substrates is involved in signal transduction by the kit-encoded receptor," EMBO J. 10, 647–654, 1991
[32]. J. Lennartsson and L.Rönnstrand, "Stem cell factor receptor/c-Kit: from basic science to clinical implications," Physiol. Rev. 92,1619–49, 2012
[33]. P. Besmer, J. E. Murphy, P. C. George, F. Qiu, P.J. Bergold, L. Lederman, H. W. Snyder Jr, D. Brodeur, E. E. Zuckerman, and W. D. Hardy, "A new acute transforming feline retrovirus and relationship of its oncogene v-kit with the protein kinase gene family," Nature, 320, 415–421, 1986
[34]. L. Escribano, M. Ocqueteaub, J. Almeida, A.Orfao, and J. F. S. Migue, "Expression of the c-kit (CD117) Molecule in Normal and Malignant Hematopoiesis," Leuk. and Lymph., 30,5-6, 459-466, 1998
[35]. E. Paietta, O. Goloubeva, D. Neuberg, J.M. Bennett, R. Gallagher, J. Racevskis, G.Dewald, P.H. Wiernik, and M.S. Tallman, "A surrogate marker profile for PML/RAR alph expressing acute promyelocytic leukemia and the association of immunophenotypic markers with morphologic and molecular subtypes," Cytometry B. Clin. Cytom. 59. 1–9.2004
[36]. A.S.Tsao, H.Kantarjian, D.Thomas,et al.,"C-kit receptor expression in acute leukemias-association with patient and disease characteristics and with outcome,"Leuk.Res.,28(4)373-378,2004
[37]. S.J. Wells, R.A. Bray, L.L. Stempora, and D.C. Farhi, "CD117/CD34 expression in leukemic blasts," Am J. Clin. Pathol.,106, 192–5,1996
[38]. A.S. Advani, "Targeting the c -kit receptor in the treatment of acute myelogenous leukemia," Curr. Hematol. Malig. Rep., **1,** 101–107,2006
[39]. C. P. Hans, W. G. Finn, T. P. Singleton, B Schnitzer, and C. W. Ross, "Usefulness of anti-CD117 in the flow cytometric analysis of acute leukemia," Am. J. of clin. Path., *117*(2), 301–305. (2002).

[40]. P. Bravo, B.D. Agustín, C. Bellas, D. González, C. Cámara, I.F. Fuertes, J. Almeida, R.G. Sanz, A. Orfao, and L. Escribano. "Expression of high amounts of the CD117 molecule in a case of B-cell non-Hodgkin's lymphoma carrying the t (14:18) translocation," Am. J. Hematol., 63(4), 226-9, Apr 2000
[41]. L.Z. Ling, Y.H. Ni, Y.L. Hu, *et al*., "Characteristics of C-Kit$^+$ cells derived from the human fetal liver,"J. Clin.Rehabi.Tiss.Eng.Re.,13(1),111-116,2009
[42]. H.R. Rodewald, K. Kretzschmar, W. Swat, and S. Takeda, "Intrathymically expressed c-kit ligand (stem cell factor) is a major factor driving expansion of very immature thymocytes *in vivo*," Immunity, 3,313–9, 1995
[43]. P. D. Nagel, A. Stenzinger, F. M. Feld, M. D. Herrmann, S. Brüderlein, T. F. Barth, *et al*., "KIT mutations in primary mediastinal B-cell lymphoma," Blood can. J., *4*(8), e241,2014
[44]. A. Pinto, A.Gloghini, V.Gattei, *et al*.,"Expression of the c-kit receptor in humun lymphoma as is restricted to Hodgkin's Disease and CD30$^+$ anaplastic large cell lymphomas," Blood.83(3),785-792,1994
[45]. E. Vakiani, G. Cattoretti, A.I. Colovai, V.V. Murty, B. Alobeid, and G. Bhagat, "CD117 expression in diffuse large B-cell lymphomas: fact or fiction? ," Pathol Int.,55(11),716-23, Nov 2005
[46]. M. Raeisi, A. R. Nikhanfar, B. Nejate, A. A. Movassaghpour Akbari, R. Dolatkhah, Y. Roosta, and Z. Sanaat, "Role of CD135/CD117 on Prognosis and Overall Survival of Acute Myeloid Leukemia," Asi. Pac. J of can. Pre., *APJCP*, *20*(9),2625–2631, 2019
[47]. E.P. Noronha, F.G. Andrade, C. Zampier, *et al*., "Immunophenotyping with CD135 and CD117 predicts the FLT3, IL-7R and TLX3 gene mutations in childhood T-cell acute leukemia," Blood Cells Mol Dis., 57,74–80,2016
[48]. S.K. Sharawat, R. Gupta, V. Raina, *et al*., "Increased co expression of c-KIT and FLT3 receptors on myeloblasts: independent predictor of poor outcome in pediatric acute myeloid leukemia," Cyto.B Clin Cytom., 84 ,390–7, 2013