ORIGINAL ARTICLE

Important Biomarkers of Diagnostic and Prognostic Significance in AML Patients

Walaa N.Roushdy [a,*], Asmaa Mahmoud [b,*], Hend A.Yassin [a]

[a] Department of Medical Biochemistry, Faculty of Medicine, Alexandria University, Alexandria, Egypt
[b] Department of Internal Medicine (Hematology Unit), Faculty of Medicine, Alexandria University, Alexandria, Egypt

Abstract

Background: ***The diagnosis of Acute Myeloid Leukemia (AML) involves a comprehensive evaluation, including the morphology of myeloid cells, immunophenotypic characteristics, conventional cytogenetics, and genetic abnormalities in bone marrow and peripheral blood. Recent advances in genomics and other technologies have greatly enhanced our understanding of AML, revealing specific mutations, gene expression patterns, and epigenetic modifications that emphasize the disease's heterogeneity. As a result, several biomarkers are becoming increasingly important for prognosis and treatment decisions. Integrating these biomarkers into diagnostic panels is essential for improving clinical outcomes, facilitating precise risk stratification, and supporting individualized treatment approaches.***

Aim of the Study: ***This study aims to evaluate the relationship between certain biomarkers in AML patients and controls using the ELISA technique.***

Methods: ***The study included 60 de novo AML patients from Alexandria University Hospitals and 60 matched controls based on age and sex.***

Results: ***To improve treatment responses and address resistance in AML, we assessed several emerging biomarkers with diagnostic and therapeutic potential. The study showed a significant relationship between these biomarkers in AML patients and controls, using the ELISA technique. This simple, reliable method could be implemented in diagnostic panels for newly diagnosed AML patients to guide treatment decisions.***

Conclusions: ***Our study demonstrates the significance of various biomarkers in AML patient assessment. These biomarkers hold considerable promise for improving diagnostic accuracy and therapeutic strategies, highlighting their potential role in optimizing AML management and enhancing patient outcomes.***

Keywords: AML; Prognosis; theraputic target; Elisa

1. Introduction

Acute myeloid leukemia (AML) is one type of hematologic malignancy characterized by the rapid proliferation of myeloid progenitor cells in the bone marrow and peripheral blood, leading to the disruption of normal hematopoiesis and resultant symptoms of anemia, bleeding, and infection. In Egypt, the incidence of AML reflects a notable burden on the healthcare system.[1]

Acute myeloid leukemia (AML) is a complex and heterogeneous malignancy characterized by a wide array of cytogenetic and molecular abnormalities that define various subgroups of the disease. Advances in treatment options have led to the development of targeted therapies tailored to these specific molecular subgroups, offering new avenues for managing AML.[2,3]

However, the treatment landscape remains challenging, particularly for patients with high-risk AML. These patients often face poor prognoses, highlighting the need for ongoing research and development of novel therapeutic strategies to improve outcomes in this difficult-to-treat population.[4]

Bisphenol A (BPA) is one kind of synthetic chemical widely used in manufacturing polycarbonate plastics and epoxy resins, which are prevalent in items such as water bottles and food can linings. Emerging studies have raised concerns about BPA's potential impact on health, including its possible link to the development of acute myeloid leukemia (AML).[5]

Accepted 19 December 2024.
Available online 31 March 2025

* Corresponding author at: Internal Medicine (Hematology Unit), Faculty of Medicine, Alexandria University, Alexandria, Egypt.
E-mail address: asmaa.hassan@alexmed.edu.eg (A. Mahmoud).

https://doi.org/10.21608/aimj.2025.446457

Studies have shown that BPA can interfere with normal cellular processes and contribute to genetic mutations, which are pivotal in the onset of leukemia. Its endocrine-disrupting properties may also alter hematopoietic stem cell function, creating a conducive environment for the development of malignancies like AML.[6]

Cytokine deregulation plays a significant role in the progression of acute myeloid leukemia (AML). Cytokines are typically released in response to cellular stresses induced by cancer, infection, and inflammation to help regulate these conditions. Interleukin-6 (IL-6) is a key cytokine involved in numerous regulatory pathways related to inflammation and immune responses. It plays a critical role in AML by promoting tumor cell proliferation, preventing apoptosis, facilitating metastasis, and influencing cancer cell metabolism, thereby contributing to the malignancy's progression and resistance to treatment.[7-9]

The activation of STAT3 by IL-6 is associated with increased therapeutic resistance in numerous tumors, including acute myeloid leukemia (AML), through the induction of mechanisms that support cell survival and proliferation.[7,8]

Cyclin D1 is indeed a key player in regulating the cell cycle, particularly in the transition from the G1 phase to the S phase, which is crucial for cell proliferation. In normal cells, Cyclin D1 levels and activity are tightly controlled to ensure proper cell division and prevent unchecked growth.[10] There are several D cyclins (D1, D2 and D3) that play an important role in the entrance of the cell into S-phase and G1 progression. There is a negative correlation between the level of cyclin D1 and the proliferation characteristic of leukemic cells.[11]

Certain cytogenetic markers and genetic mutations are strongly linked to risk stratification and prognosis, and they are now part of the World Health Organization's classification of AML. There are two primary apoptotic pathways: the extrinsic and intrinsic pathways. The extrinsic pathway is driven by a set of cell surface receptors, including FAS (CD95) and the tumor necrosis factor-related apoptosis-inducing ligand receptors TRAIL-R1 (DR4). Upon binding to their specific ligands, these receptors initiate an intracellular signaling cascade that activates caspase 8 and other caspases, ultimately resulting in apoptotic cell death.[12]

The aim of the study was to evaluate the levels of Bisphenol A (BPA), Interleukin 4 (IL-4), Interleukin 6 (IL-6), Cyclin D1, BAD (Bcl-2 Antagonist of Cell Death), and FAS (Apoptosis-mediating Surface Antigen, TNF Receptor Superfamily Member 6) in patients with Acute Myeloid Leukemia (AML).

2. Patients and methods

he study enrolled 120 subjects divided into two groups:

Group I: composed of 60 adult newly diagnosed acute myeloid leukemia patients, aged from 18 years to below 60 years, recruited from the hematology Unit, Internal Medicine department, Alexandria University Hospitals.

Group II: composed of 60 healthy age and sex matched subjects as controls.

The following subjects were excluded from the study: pregnant female subjects, subjects with concomitant chronic disease, patients with acute promyelocytic anemia – M3, and patients with associated other malignancies.

All patients were subjected to a detailed medical history and physical examination.

Sampling: Six ml of venous blood was drawn from every patient and control subject. Each blood sample was then divided into two aliquots; a plain tube and an EDTA tube. In the plain tube, blood was centrifuged at 1200 xg for 10 minutes o separate serum sample, which was kept frozen at -20oC until use.

The following laboratory investigations were performed:

Complete Blood Count and morphological studies:[13]

Kidney Function tests and Liver Function tests by the colorimetric method.[14-16]

Bone marrow aspiration was done for morphological studies, cytogenetics and immunophenotyping.

Determination of serum levels of bisphenol A (BPA), interleukin-4, interleukin-6, cyclin D1, Bad and Fas using solid phase standard sandwich enzyme linked immunosorbent assay (ELISA): Commercially available ELISA kits were used to measure the serum levels of bisphenol A (Cat. No.: BZEK1424. Chongqing Biospes CO. China. Website: www.biospes.com), IL-4 (Cat. No.: E-EL-H0101. Elabscience CO. USA. Website: www.elabscience.com), IL-6 (Cat. No.: D6050. Bio-Techne CO. USA. Website: www.bio-techne.com), cyclin D1 (Catalog No.: HUFI00736. Assay Genie CO. Ireland. Website: www.ASSAYGenie.com), Bad (Catalog No.: LS-F10913. LSBio CO. USA. Website: www.LSBio.com) and Fas (Catalog No.: E-EL-H6196. Elabscience CO. USA. Website: www.elabscience.com) following the manufacturer's instructions.

Statistical Analysis: Data were fed into the computer and analyzed using IBM SPSS software version 20.0 (Armonk, NY: IBM Corp). The Chi-square test was used to compare two groups. Continuous data were first assessed for normality using the Kolmogorov-Smirnov test. Quantitative data were reported as the range (minimum and

maximum), mean, standard deviation, median, and interquartile range (IQR). For normally distributed quantitative variables, the Student's t-test was employed to compare two groups. For non-normally distributed quantitative variables, the Mann-Whitney test was used. Statistical significance was determined at the 5% level.

3. Results

This study enrolled a total of 120 subjects divided into 60 newly diagnosed AML patients and 60 healthy individuals of matched demographic criteria. The leukemic patients consisted of 36 (60%) female and 24 (40%) male patients, whereas the control group comprised of 43 (71.7%) female and 17 (28.3%) male patients. Regarding CBC measurement, there was a statistically significant difference between cases and controls as illustrated in table 1.

We illustrated in table (2) patient distribution according to FAB classification, blast percentage at diagnosis median was (78%), cytogenetics and risk stratification and response to standard chemotherapeutic regimen (3+7) protocol after which 20% of AML patients achieved complete remission, 5% responded partial to treatment and 31% was refractory to treatment.

As shown in table (3) we studied some of the major biomarkers in AML patients, Mean for Bisphenol A (690.3 ± 122.3) in patients group while in control group (257.4 ± 87.05) , FAS (5.73 ± 1.45) while in control group (2.68 ± 0.74), IL4 (101.5 ± 36.31) in patients group while (35.24 ± 13.83) in control group, IL6 (36.90 ± 9.94) in patients group while in control group (13.40 ± 6.95), cyclin D1 mean was (9.36 ± 2.02) in patients group while (3.42 ± 1.46) in control group and for Bad mean was (1.43 ± 0.46) in patients group and (2.63 ± 0.80) in control group. All markers were statistically significant with p-value less than 0.05.

We used ROC curve to assess Diagnostic performance for different parameters in our study to discriminate patients (n = 60) from control (n = 60) as shown in table (4) and figure (1).

Table 1. Comparison between Patients and control groups according to demographic and laboratory data

	CASES (N = 60)	CONTROL (N = 60)	TEST OF SIG.	P
SEX				
MALE	24 (40.0%)	17 (28.3%)	x^2= 1.815	0.178
FEMALE	36 (60.0%)	43 (71.7%)		
AGE (YEARS)				
MIN. – MAX.	18 – 59	18 – 58	t= 0.694	0.489
MEAN ± SD.53	38.45 ± 10.55	37.12 ± 10.51		
MEDIAN (IQR)	37 (30 – 46.50)	36 (30 – 44.50)		
HB				
MIN. – MAX.	6.0 – 10.20	10.50 – 14.60	t= 21.376*	<0.001*
MEAN ± SD.	7.88 ± 1.06	12.12 ± 1.11		
MEDIAN (IQR)	7.95 (7.0 – 8.55)	12.0 (11.30 – 12.60)		
WBCS				
MIN. – MAX.	1.62 – 116.7	4.0 – 6.50	U= 115.00*	<0.001*
MEAN ± SD.	37.17 ± 29.05	4.91 ± 0.69		
MEDIAN (IQR)	32.0 (14.48 – 49.50)	4.80 (4.30 – 5.30)		
PLATELETS				
MIN. – MAX.	11.0 – 81.0	165.0 – 330.0	t= 33.447*	<0.001*
MEAN ± SD.	49.67 ± 16.78	254.4 ± 44.33		
MEDIAN (IQR)	50.0 (36.0 – 63.0)	250.0 (220.0 – 288.50)		
CREATININE				
MIN. – MAX.	0.50 – 1.20	0.35 – 1.10	U= 1143.50*	0.001*
MEAN ± SD.	0.86 ± 0.21	0.72 ± 0.17		
MEDIAN (IQR)	0.90 (0.70 – 1.0)	0.65 (0.60 – 0.84)		
UREA				
MIN. – MAX.	8.0 – 68.48	15.0 – 35.0	U= 951.000	<0.001*
MEAN ± SD.	31.40 ± 10.65	23.57 ± 5.46		
MEDIAN (IQR)	32.0 (23.0 – 40.11)	23.0 (19.50 – 27.0)		
ALT				
MIN. – MAX.	17.0 – 65.0	10.0 – 43.0	U= 443.00*	<0.001*
MEAN ± SD.	35.58 ± 14.46	18.75 ± 8.27		
MEDIAN (IQR)	31.50 (24.50 – 44.0)	16.0 (13.50 – 20.0)		
AST				
MIN. – MAX.	16.0 – 88.0	8.0 – 25.0	U= 121.50*	<0.001*
MEAN ± SD.	29.67 ± 10.49	13.87 ± 4.22		
MEDIAN (IQR)	29.0 (22.0 – 33.50)	13.0 (10.0 – 16.0)		

Table 2. Distribution of results of patients according to different hematological parameters (n = 60)

	NO. (%)
FAB	
0	2 (3.3%)
1	20 (33.3%)
2	4 (6.7%)
4	13 (21.7%)
5	21 (35.0%)
BLASTS	
MIN. – MAX.	28.0 – 97.0
MEAN ± SD.	72.82 ± 17.07
MEDIAN (IQR)	78.0 (60.50 – 85.50)
FLT3	
NEGATIVE	59 (98.3%)
POSITIVE	1 (1.7%)
CYTOGENETIC	
NO META	19 (31.7%)
NORMAL	28 (46.7%)
ABNORMAL	13 (21.7%)
TRANS 3,3	1 (7.7%)
47, MARCH	2 (15.4%)

MON X TRANS 9,22	1 (7.7%)
45 DEL Y ,TRANS 8 21	1 (7.7%)
46 XY, DEL (11)Q(23)	1 (7.7%)
46 XY, DEL (3) (Q21) T 1;1), T (2;7)	1 (7.7%)
48 XX +22	1 (7.7%)
46 XY, INV (9)(Q23Q34)	1 (7.7%)
47 XY +8	1 (7.7%)
COMPLEX	1 (7.7%)
MONOSOMY 19	1 (7.7%)
RISK STRATIFICATION	(n = 41)
LOW RISK	1 (2.4%)
INTERMEDIATE RISK	33 (80.5%)
HIGH RISK	7 (17.1%)
NPM	
NEGATIVE	55 (91.7%)
POSITIVE	5 (8.3%)
RESPONSE TO R	
COMPLETE REMISSION	12 (20.0%)
PARTIAL REMISSION	3 (5.0%)
REFRACTORY	19 (31.7%)
DIED	19 (31.7%)
LOST IN FOLLOW-UP	7 (11.7%)

Table 3. Comparison between patients and control groups according to studied biochemical parameters

	CASES (N = 60)	CONTROL (N = 60)	P
BISPHENOL-A (MG/ML)			
MEAN ± SD.	690.3 ± 122.3	257.4 ± 87.05	<0.001*
FAS (NG/ML)			
MEAN ± SD.	5.73 ± 1.45	2.68 ± 0.74	<0.001*
IL-4 (PG/ML)			
MEAN ± SD.	101.5 ± 36.31	35.24 ± 13.83	<0.001*
IL-6 (PG/ML)			
MEAN ± SD.	36.90 ± 9.94	13.40 ± 6.95	<0.001*
CYCLIN-D1(NG/ML)			
MEAN ± SD.	9.36 ± 2.02	3.42 ± 1.46	<0.001*
BAD (NG/ML)			
MEAN ± SD.	1.43 ± 0.46	2.63 ± 0.80	<0.001*

Table 4. Diagnostic performance for different parameters to discriminate patients (n = 60) from control (n = 60)

	AUC	P	95% C.I	CUT OFF	SENSITIVITY	SPECIFICITY	PPV	NPV
BISPHENOL-A (MG/ML)	0.985	<0.001*	0.966 – 1.000	>340	95.00	90.00	90.5	94.7
FAS (NG/ML)	0.923	<0.001*	0.862 – 0.984	>3.5	91.67	91.67	91.7	91.7
IL-4 (PG/ML)	0.964	<0.001*	0.933 – 0.995	>37.4#	96.67	91.67	92.1	96.5
IL-6 (PG/ML)	0.979	<0.001*	0.954 – 1.000	>18	96.67	90.0	90.6	96.4
CYCLIN-D1 (NG/ML)	0.966	<0.001*	0.939 – 0.994	>5	93.33	73.33	77.8	91.7
BAD (NG/ML)	0.897	<0.001*	0.841 – 0.953	≤1.9	83.33	81.67	82.0	83.1

AUC: Area Under a Curve p value: Probability value CI: Confidence Intervals

NPV: Negative predictive value PPV: Positive predictive value

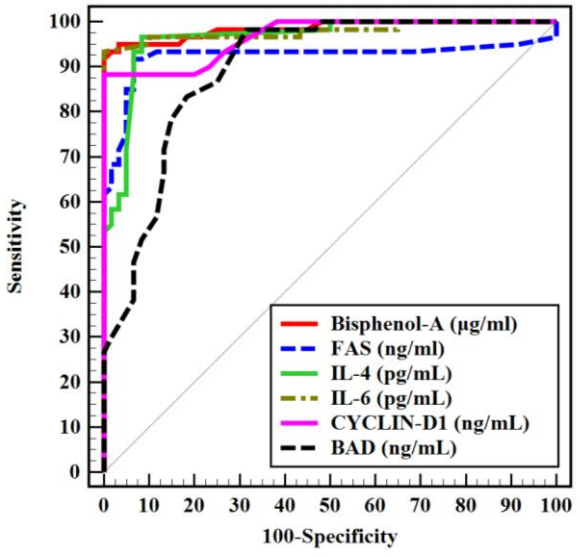

Figure 1. ROC curve for different parameters to discriminate patients (n = 60) from control (n = 60)

4. Discussion

Acute Myeloid Leukemia (AML) is a complex heterogeneous clonal disease characterized by abnormal hematopoietic progenitors, and biomarkers play a crucial role in its management.[17]

Here we focused on some of most important biomarkers in AML, Bisphenol A (BPA), commonly found in human serum, has been shown to promote the proliferation of AML cells and reduce their sensitivity to some chemotherapy agents like DNR and Ara-C which are corner stone in AML treatment. This finding is also reported by Z. J. Chen et al and K.-S. Khan et al. [6, 18]

Mileva et al. and Pivnenko et al. explained the direct exposure of humans to biphenolic materials in many industrial products. This leads to many changes in the human body, as stated by Mileva et al. which showed epigenetic changes that happen to humans, which also affect the signaling pathway of cells, which is connected to carcinogenesis.[19, 20]

Most of the studies measured Fas (CD95) by flow cytometry in peripheral blood and bone marrow cells with a range of expression (1.5–5.1). In our study, we measured FAS using the ELISA technique to provide a cheaper method for evaluation with comparable results to other techniques. Furthermore, it has been confirmed by our study that FAS expression was significantly lower in the AML patients group compared to the

controls which in line with results of Prada-Arismendy et al Chen et al.[18,21] Reduced expression of molecules like FAS that play a role in triggering the apoptotic pathway helps cancer cells escape (apoptosis) programmed cell death. Consistent with our findings, this downregulation likely supports the survival and unchecked growth of cancer cells, allowing them to evade therapies that aim to induce apoptosis.

Peña-Martínez et al discussed the major role of IL4 in the AML microenvironment as it induces apoptosis of AML cells. Additionally, IL4 is a negative regulator of growth and survival of Myeloid leukemic stem cells.[22] This goes with our results, which have shown a significant difference between AML patients and controls. Lundin J et al conducted a phase I/II study and found that administration of IL4 might induce antiapoptotic effect on leukemic cells.[23] But other researcher considered blocking IL 4 and its receptor is one of theraputic targets in AML treatment as it is considered tumor promoting.[24-26] This contradictory opinions raise the need for further evaluation of the role of IL4 in AML patients using murine models.

High relapse rate and poor survival are principally related to chemo resistance in AML patients. Many cytokines have been studied for their pivotal role in chemoresistance, and one of them is IL-6. Hou et al and Saadi et al concluded from their studies that IL6 confers chemo resistance by different mechanisms, such as MFN1-mediated mitochondrial fusion and promotion of the oxidative phosphorylation pathway (OXPHOS).[8, 27]

Cyclin D1 role as oncogenic driver in many tumors including AML remains of great debate. In agreement with our study results, which showed a significant relationship between the patient group and controls in newly diagnosed AML patients, which plays a major role as oncogenic drivers, as reported by Masamoto et al.[28] The function of cyclin D1 and its associated kinases seems diverse and still poorly understood in AML. New CDK inhibitors such as ribociclib, abemaciclib and others are trying to join the guidelines for cancer treatment.[29-31]

Garcia et al emphasized the fact that treatment of AML has remained a big challenge till now, with the standard model of chemotherapy approach for eligible patients. In 2017, with the advancement in research, the FDA approved two targeted therapies for AML patients with a molecular alteration in the FLT3 or IDH genes. IN 2020, another Major advancement was made with the release of the efficacy of VEN for the treatment of AML patients who are not eligible for intensive treatment. Targeting the BAD pathway has made a major change in AML treatment plans, which goes with our results, as there is a significant difference between levels of BAD.[32-34]

4. Conclusion

In this study, we provide an economic, simple and easy approach to a number of significant biomarkers playing a role either in tumorigenesis, cell cycle regulation and apoptosis of cancer cells and pave the road for Urge need for targeting these biomarkers and initiating clinical trial to change AML treatment plan for better achievement of treatment goals.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Authorship

All authors have a substantial contribution to the article

Funding

No Funds : Yes

Conflicts of interest

There are no conflicts of interest.

References

1. Yang X, Wang J. Precision therapy for acute myeloid leukemia. J Hematol Oncol. 2018;11(1):3.
2. Bhansali RS, Pratz KW, Lai C. Recent advances in targeted therapies in acute myeloid leukemia. J Hematol Oncol. 2023;16(1):29.
3. Fleischmann M, Schnetzke U, Hochhaus A, Scholl S. Management of Acute Myeloid Leukemia: Current Treatment Options and Future Perspectives. Cancers (Basel). 2021;13(22).
4. Horibata S, Alyateem G, DeStefano CB, Gottesman MM. The Evolving AML Genomic Landscape: Therapeutic Implications. Curr Cancer Drug Targets. 2020;20(7):532-544.
5. Zhang S, Li J, Fan J, Wu X. Bisphenol A triggers the malignancy of acute myeloid leukemia cells via regulation of IL-4 and IL-6. J Biochem Mol Toxicol. 2020;34(1):e22412.
6. Khan NG, Correia J, Adiga D, Rai PS, Dsouza HS, et al. A comprehensive review on the carcinogenic potential of bisphenol A: clues and evidence. Environ Sci Pollut Res Int. 2021;28(16):19643-19663.
7. Zhang Y, Guo H, Zhang Z, Lu W, Zhu J, et al. IL-6 promotes chemoresistance via upregulating CD36 mediated fatty acids uptake in acute myeloid leukemia. Exp Cell Res. 2022;415(1):113112.
8. Saadi MI, Ramzi M, Hosseinzadeh M, Ebrahimi N, Owjfard M, et al. Expression Levels of Il-6 and Il-18 in Acute Myeloid Leukemia and Its Relation with Response to Therapy and Acute GvHD After Bone Marrow Transplantation. Indian J Surg Oncol. 2021;12(3):465-471.
9. Mauer J, Denson JL, Brüning JC. Versatile functions for IL-6 in metabolism and cancer. Trends Immunol. 2015;36(2):92-101.
10. Montalto FI, De Amicis F. Cyclin D1 in Cancer: A Molecular Connection for Cell Cycle Control, Adhesion and Invasion in Tumor and Stroma. Cells. 2020;9(12):2648.
11. Jaroslav P, Martina H, Jirí S, Hana K, Petr S, et al. Expression of cyclins D1, D2, and D3 and Ki-67 in Leukemia. Leuk Lymphoma. 2005;46(11):1605-1612.

12.Min YJ, Lee JH, Choi SJ, Chi HS, Lee JS, et al. Prognostic significance of Fas (CD95) and TRAIL receptors (DR4/DR5) expression in acute myelogenous leukemia. Leuk Res. 2004;28(4):359-365.
13.Bain BJ, Bates I, Laffan MA. Dacie and Lewis Practical Haematology. 12th ed. New York: Elsevier 2017.
14.Kaplan LA, Pesce AJ, Kazmierczak SC. Clinical Chemistry: Theory, Analysis, and Correlation 4th ed. St. Louis: Mosby; 2003.
15.Coulombe JJ, Favreau L. A new simple semimicro method for colorimetric determination of urea. Clin Chem. 1963;9:102-108.
16.Burtis CA, Ashwood ER, Bruns DE. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. London: Elsevier Health Sciences; 2011.
17.Bhatia K, Sandhu V, Wong MH, Iyer P, Bhatt S. Therapeutic biomarkers in acute myeloid leukemia: functional and genomic approaches. Front Oncol. 2024;14:1275251.
18.Chen ZJ, Yang XL, Liu H, Wei W, Zhang KS, et al. Bisphenol A modulates colorectal cancer protein profile and promotes the metastasis via induction of epithelial to mesenchymal transitions. Arch Toxicol. 2015;89(8):1371-1381.
19.Pivnenko K, Pedersen GA, Eriksson E, Astrup TF. Bisphenol A and its structural analogues in household waste paper. Waste Manag. 2015;44:39-47.
20.Mileva G, Baker SL, Konkle AT, Bielajew C. Bisphenol-A: epigenetic reprogramming and effects on reproduction and behavior. Int J Environ Res Public Health. 2014;11(7):7537-7561.
21.Prada-Arismendy J, Arroyave JC, Röthlisberger S. Molecular biomarkers in acute myeloid leukemia. Blood Rev. 2017;31(1):63-76.
22.22. Peña-Martínez P, Eriksson M, Ramakrishnan R, Chapellier M, Högberg C, et al. Interleukin 4 induces apoptosis of acute myeloid leukemia cells in a Stat6-dependent manner. Leukemia. 2018;32(3):588-596.
23.Lundin J, Kimby E, Bergmann L, Karakas T, Mellstedt H, et al. Interleukin 4 therapy for patients with chronic lymphocytic leukaemia: a phase I/II study. Br J Haematol. 2001;112(1):155-160.
24.Bankaitis KV, Fingleton B. Targeting IL4/IL4R for the treatment of epithelial cancer metastasis. Clin Exp Metastasis. 2015;32(8):847-856.
25.Venmar KT, Carter KJ, Hwang DG, Dozier EA, Fingleton B. IL4 receptor ILR4α regulates metastatic colonization by mammary tumors through multiple signaling pathways. Cancer Res. 2014;74(16):4329-4340.
26.Puri RK, Leland P, Kreitman RJ, Pastan I. Human neurological cancer cells express interleukin-4 (IL-4) receptors which are targets for the toxic effects of IL4-Pseudomonas exotoxin chimeric protein. Int J Cancer. 1994;58(4):574-581.
27.Hou D, Zheng X, Cai D, You R, Liu J, et al. Interleukin-6 Facilitates Acute Myeloid Leukemia Chemoresistance via Mitofusin 1-Mediated Mitochondrial Fusion. Mol Cancer Res. 2023;21(12):1366-1378.
28.Masamoto Y, Chiba A, Mizuno H, Hino T, Hayashida H, et al. EVI1 exerts distinct roles in AML via ERG and cyclin D1 promoting a chemoresistant and immune-suppressive environment. Blood Adv. 2023;7(8):1577-1593.
29.Sledge GW, Jr., Toi M, Neven P, Sohn J, Inoue K, et al. The Effect of Abemaciclib Plus Fulvestrant on Overall Survival in Hormone Receptor-Positive, ERBB2-Negative Breast Cancer That Progressed on Endocrine Therapy-MONARCH 2: A Randomized Clinical Trial. JAMA Oncol. 2020;6(1):116-124.
30.Tripathy D, Im SA, Colleoni M, Franke F, Bardia A, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. Lancet Oncol. 2018;19(7):904-915.
31.Richter A, Schoenwaelder N, Sender S, Junghanss C, Maletzki C. Cyclin-Dependent Kinase Inhibitors in Hematological Malignancies-Current Understanding, (Pre-) Clinical Application and Promising Approaches. Cancers (Basel). 2021;13(10):2497.
32.Kantarjian H, Kadia T, DiNardo C, Daver N, Borthakur G, et al. Acute myeloid leukemia: current progress and future directions. Blood Cancer J. 2021;11(2):41.
33.DiNardo CD, Jonas BA, Pullarkat V, Thirman MJ, Garcia JS, et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. N Engl J Med. 2020;383(7):617-629.
34.Garciaz S, Miller T, Collette Y, Vey N. Targeting regulated cell death pathways in acute myeloid leukemia. Cancer Drug Resist. 2023;6(1):151-168.