Infection and Drug Resistance

Dovepress
open access to scientific and medical research

Open Access Full Text Article

CASE REPORT

Carrimycin in a Patient with Acute Myeloid Leukemia Complicated with Life-Threatening Mixed Perianal Infection: A Case Report and Literature Review

Xiawan Yang[1–3,*], Yingying Shen[1–3,*], Tonglin Hu[1–3], Hangchao Li[1–3], Yun Zhang[1–3], Yiping Shen[1–3], Dijiong Wu[1–4]

[1]Department of Hematology, The First Affiliated Hospital of Zhejiang Chinese Medical University (Zhejiang Provincial Hospital of Chinese Medicine), Hangzhou, Zhejiang, People's Republic of China; [2]The First School of Clinical Medicine, Zhejiang Chinese Medical University, Hangzhou, Zhejiang, People's Republic of China; [3]National Traditional Chinese Medicine Clinical Research Base (Hematology), Hangzhou, Zhejiang, People's Republic of China; [4]Department of Oncology and Hematology, Wenzhou Hospital of Integrated Traditional Chinese and Western Medicine Affiliated to Zhejiang Chinese Medicine University, Wenzhou, Zhejiang, People's Republic of China

*These authors contributed equally to this work

Correspondence: Dijiong Wu; Yiping Shen, Department of Hematology, The First Affiliated Hospital of Zhejiang Chinese Medical University (Zhejiang Provincial Hospital of Chinese Medicine), Youdian Road No. 54, Hangzhou, 310006, Zhejiang, People's Republic of China, Tel +86-0571-86620325, Email wudijiong@zcmu.edu.cn; shenyp_@126.com

Background: Perianal infection has a high incidence and mortality rate in patients with acute myeloid leukemia (AML). Sometimes there is a lack of effective anti-infective treatment regimens.

Case Presentation: A 58-year-old male diagnosed with AML presented with secondary perianal infection and septic shock upon admission. Although multiple pathogen cultivation and antibiotic sensitivity tests indicated the presence of sensitive strains, the corresponding antibiotics were ineffective. As a last resort, carrimycin was introduced, ultimately controlling the infection and leading to disease remission.

Conclusion: Carrimycin is a complementary treatment option when conventional antibiotic therapy fails. It operates through multiple mechanisms beyond its antibiotic properties and warrants further investigation.

Keywords: carrimycin, perianal infection, acute myeloid leukemia, immunomodulatory

Introduction

Perianal infections are common complications in patients with acute myeloid leukemia (AML), particularly during the bone marrow suppression phase. Immunodeficiency, barrier damage, and anatomical location further facilitate the occurrence of perianal infection, with an incidence of 9.2%–27%.[1,2] Perianal infection is often accompanied by severe pain, swelling, and constipation, affecting the patients' quality of life.[3,4] In severe cases, it may endanger the patient's life, with a mortality rate as high as 16%.[5]

The most frequently detected pathogens in patients with perianal infections are *Escherichia coli, Enterococcus, Bacteroides*, and *Klebsiella pneumoniae* in descending order of pathogenicity.[2,6,7] Pathogen cultivation and antibiotic sensitivity tests can be used to guide the selection of antibiotics. However, even in the antibiotic-sensitive strains, the efficacy is not always ideal in patients with severe bone marrow suppression, which greatly increases the difficulty of treatment.

Carrimycin is a genetically engineered macrolide that has been gradually explored and tentatively applied in clinical practice for patients with ineffective therapeutic strategies.[8] In fact, it was also used during the SARS-CoV-2 pandemic,

Received: 28 April 2024
Accepted: 9 August 2024
Published: 21 August 2024

but its therapeutic efficacy was controversial. Here, we present a case of mixed perianal infection in a patient with neutropenic AML who was successfully treated with carrimycin. Additionally, we summarize and speculate on the possible mechanisms of function based on previous studies involving carrimycin.

Case Presentation

A 58-year-old male patient was admitted to our hospital with AML-M0 (intermediate risk subgroup), characterized by a chromosomal profile of 47, XY, +4, t (7;14), (q21; q32) and a FLT3-ITD mutation in c.1779_1780insGGGCCCGGGCCT with a 30.08% variant allele frequency, having previously undergone two courses of chemotherapy including venetoclax +azacytidine+sorafenib and idarubicin+azacytidine+sorafenib without achieving disease remission. He complained of severe perianal pain and fever which began five days prior to admission. The patient presented with fever (38.2°C), tachycardia (100 beats per minute), hypoxemia (90%), and hypotension (82/53 mmHg). A large ulceration, accompanied by redness and swelling of the adjacent skin, was observed in the perianal area, with tenderness noted but fluctuating sensation being absent. Laboratory examinations showed a white blood cell count of 256000/μL, neutrophil count of 100/μL, hemoglobin of 78 g/L, platelet count of 4000/μL, peripheral blast cell percent of 30%, C-reactive protein (CRP) level of 81.02 mg/dL, and procalcitonin (PCT) level of 3.14 mg/dL. β-D-glucan, galactomannan (G/GM) tests and perianal microbiome screen were negative. Pelvic MR imaging showed an anal fistula (Figure 1), and pulmonary computed tomography (CT) revealed scattered inflammation in both lungs (Supplemental Figure 1A). A subsequent bone marrow biopsy revealed a high proportion of blast cells (89%). Hence, the patient was diagnosed with AML combined with perianal infection and pneumonia.

On admission, the patient was treated with meropenem and linezolid, the antibacterial spectrum of which covered gram-positive and gram-negative bacteria, Pseudomonas, and anaerobes. Three days later, perianal skin wound secretion cultures revealed *Escherichia coli, Klebsiella pneumoniae*, and *Morganella morganii*, and antibiotic sensitivity tests showed susceptibility (Supplemental Table 1). However, the patient developed cool and moist limbs, shock, and sustained a high body temperature peak above 38°C, indicating that the infection remained uncontrolled. We switched linezolid to tigecycline and initiated empirical antifungal treatment with voriconazole. The patient was simultaneously administered aggressive supportive treatment including adequate splanchnic perfusion, vasopressors and blood product transfusions. On the 7th day, the patient's condition continued to deteriorate while repeat pulmonary CT showed significant absorption of the inflammatory lesions (Supplemental Figure 1B). Therefore, we attempted to switch the antibiotics to polymyxin and carrimycin. The following day, the patient's temperature dropped below 37°C, while the CRP and PCT values significantly decreased while neutrophil levels increased. And common adverse drug reactions, such as gastrointestinal reactions, neurological reactions, and laboratory abnormalities, were not detected. Consequently, we initiated chemotherapy with venetoclax and sorafenib. After a week of maintaining stable temperature control, with

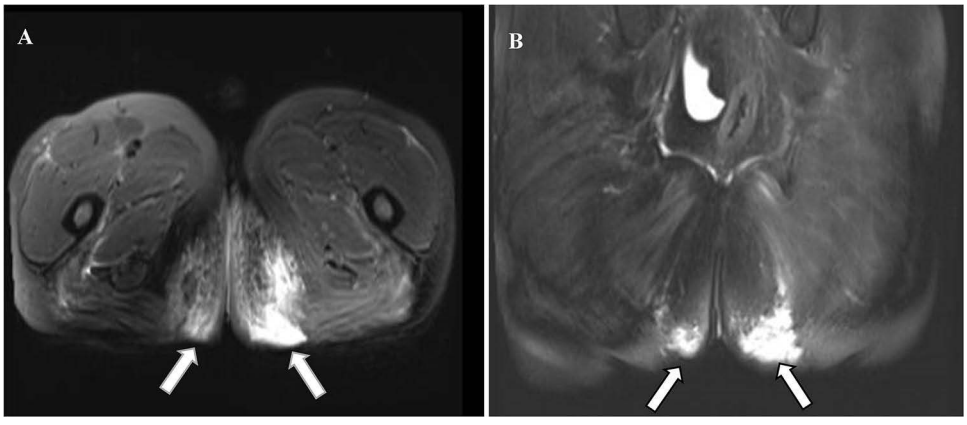

Figure 1 Pelvis MR images on admission.
Notes: Axial (**A**) and coronal (**B**) T2-weighted fat-saturated transverse images with contrast demonstrated an anal fistula, with the peripheral enhancing cystic lesion (arrow) showing inflammatory changes in the perianal region.

CRP and PCT values near normal levels, we switched from carrimycin to omycycline owing to the financial constraints faced by the patient.

On the 21st day, the temperature increased. At this point, peripheral blasts and bone marrow blasts decreased to 1% and 0.5%, respectively. A follow-up pulmonary CT scan exhibited disappearance of the inflammatory lesions (Supplemental Figure 1C). Additionally, a small amount of purulent secretion was observed around the anus, with the secretion culture indicative of *Escherichia coli* and *Klebsiella pneumoniae*. In response to the clinical deterioration, we adjusted omycycline to zavicefta while continuing polymyxin based on perianal secretion culture testing. Throughout the treatment period, debridement of perianal abscess was performed twice with the assistance of urologists. Unfortunately, after 9 days of treatment with zavicefta and polymyxin, the fever persisted and the inflammatory markers worsened. We adjusted the anti-infection regimen to polymyxin and carrimycin. Similar outcomes and indicator changes occurred within the next few days, including improvements in temperature, neutrophil count, and CRP and PCT levels. Eventually, the patient was discharged 51 days after admission, achieving complete remission of leukemia, and the perianal ulcers gradually healed with good granulation. His clinical course and perianal ulcer wounds at different time points are presented in Figures 2 and 3.

Discussion

An immunocompromised state predisposes the patients with AML to opportunistic organisms.[9] Damage to mucosal and mechanical barriers further facilitates the entry of pathogens.[10] Moreover, unlike other skin and soft tissue infections, perianal infections present unique treatment challenges because of fecal contamination and anatomical features. The patient in the reported case had unstable vital signs and symptoms of mixed perianal infection, almost meeting the diagnostic criteria for sepsis, which can seriously threaten the patient's life. Although multiple pathogen cultivation and antibiotic sensitivity tests indicated the presence of sensitive strains, the corresponding antibiotics were ineffective. Such situations are common in clinical practice. Helping these patients pass through the severe bone marrow suppression phase smoothly is an urgent problem that needs to be addressed.

Initially, carrimycin was administered tentatively. Surprisingly, both the temperature and inflammatory indicators improved by the second day, aiding in achieving chemotherapy opportunities. The same outcome was observed when the patient experienced granulocyte deficiency after chemotherapy. Even more notable was the speed at which the treatment took effect and the accompanying increase in neutrophil count. Additionally, analysis of the case reveals several interesting issues regarding possible mechanisms.

Firstly, carrimycin, a macrolide antibiotic, affects bacterial protein synthesis by inhibiting peptidyl transferase activity in 50s ribosomes. Its solubility in lipids and extended half-life afford superior penetration and retention, endowing it with more potent antibacterial effects compared to other macrolides.[11,12] This enhanced efficacy likely contributed to the rapid improvement observed the day after application in our reported case. In addition to its antibacterial properties, it exhibits immunomodulatory effects, including the attraction of neutrophils to inflammatory locations, bolstering macrophage phagocytosis,[13] and a notable increase in HLA-DR and CD8+ T cell levels, thereby modulating immune responses.[14] Remarkably, the patient demonstrated swift neutrophil count recovery following the administration of carrimycin. We hypothesized that carrimycin stimulates neutrophil maturation and release, thus reinforcing the host's immune defense and aiding in pathogen eradication. Unlike other anti-infectious drugs, it may play a crucial role in the efficacy of antibiotics in patients with severe bone marrow suppression.

Additionally, studies have shown that carrimycin exhibits antitumor activities, potentially via various regulatory pathways, such as JNK2/TIF-IA/POLI, PI3K/AKT/mTOR, and MAPK, which induce cancer cell cycle arrest and apoptosis.[15–17] Existing research on its antitumor effects primarily focuses on solid tumors, such as lung cancer, hepatocellular carcinoma, and oral squamous cell carcinoma. In our case, there was no direct evidence of carrimycin against leukemia cells. The in vivo and in *vitro* experiments will be performed in future experiments. The breadth of potential applications highlights versatility of carrimycin and underscores the need for continued research on its multi-faceted therapeutic benefits.

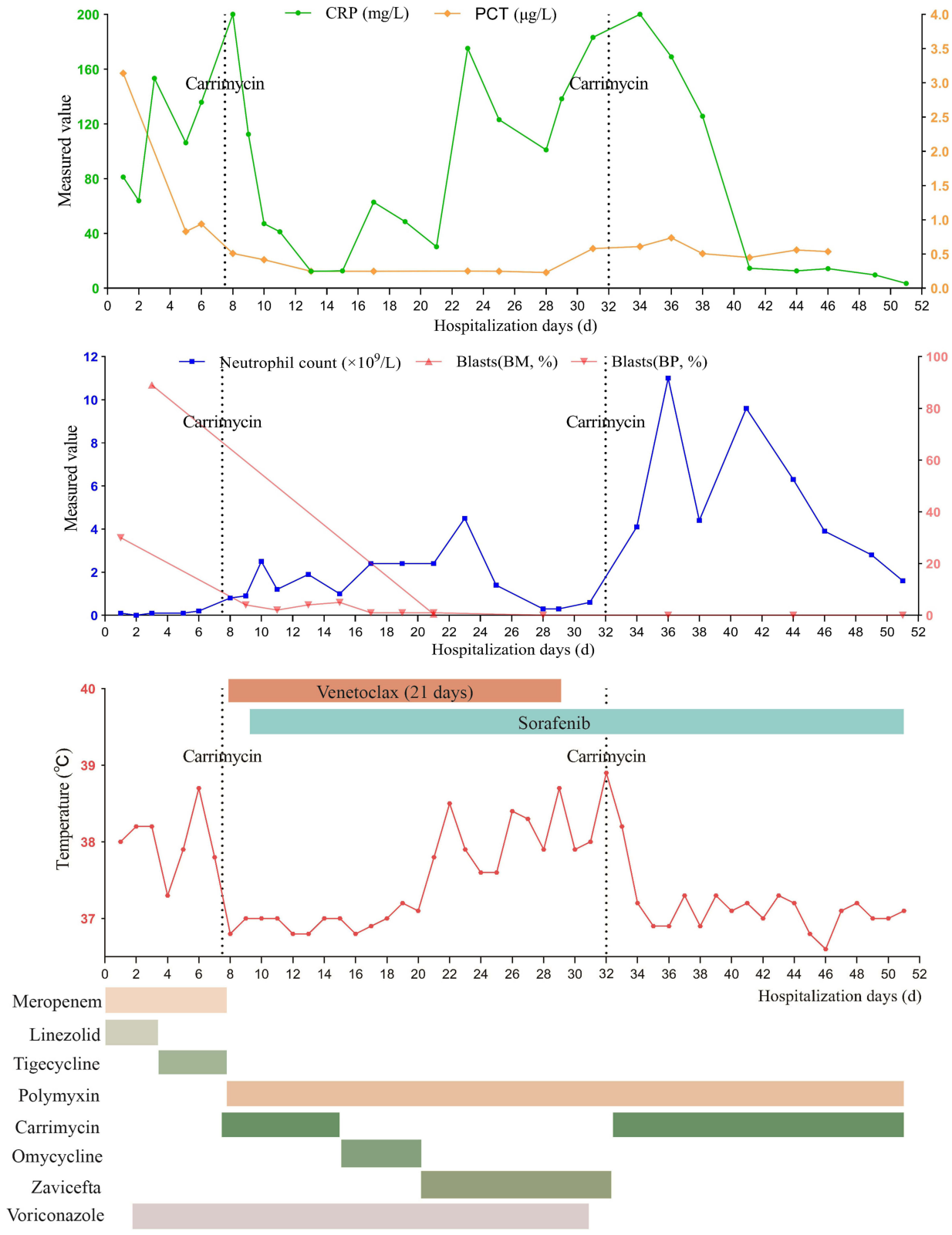

Figure 2 Clinical course.
Notes: Changes in the inflammatory factors, neutrophil count, blasts, body temperature, anti-infective and chemotherapy regimen during hospitalization.
Abbreviations: CRP, C-reactive protein; PCT, procalcitonin; BM, bone marrow; PB, peripheral blood.

Figure 3 Gross images of perianal ulcer wounds at different time points.
Notes: (**A**) A large ulceration upon admission, with adjacent skin exhibiting redness and swelling. (**B**) A ruptured perianal ulcer at the initiation of chemotherapy, with a small amount of purulent secretion. (**C** and **D**) illustrated the perianal ulcer wound after the first and second debridement, respectively. (**E** and **F**) displayed the ulcerated surface accompanied by new granulation tissue proliferation at discharge, and the wound gradually heals and crusts over during follow-up period, respectively.

Conclusion

Carrimycin has emerged as a novel treatment option when conventional antibiotic therapy fails. Our study serves as a treatment reference for similar cases. Moreover, carrimycin operates through multiple mechanisms beyond its antibiotic properties, highlighting its potential for further exploration.

Data Sharing Statement

The data used and/or analyzed during the current study are available from the corresponding author (Dijiong Wu) upon reasonable request.

Ethics Approval and Consent to Participate

This study was approved by the ethical committee of First Affiliated Hospital of Zhejiang Chinese Medical University.

Patient Consent for Publication

Written informed consent was obtained from the patient for publication of this case report and the images. Details of the case can be published without institutional approval.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

The present study was supported by the Zhejiang Provincial Natural Science Foundation (No. LY21H290003), National Natural Science Foundation of China (No. 81503296), Zhejiang Scientific Research Fund of Traditional Chinese Medicine (NO. 2020ZB085 and No.2021ZQ029), Specific Program of Scientific Research of Zhejiang Chinese Medicine University for Affiliated Hospital (NO.2023FSYYZZ04), Project of Academic Inheritance Studio of Famous and Aged Chinese Medicine Experts in Zhejiang Province (No. GZS2021022).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Rieger CT, Liss B, Mellinghoff S, et al. Anti-infective vaccination strategies in patients with hematologic malignancies or solid tumors-guideline of the infectious diseases working party (AGIHO) of the German Society for Hematology and Medical Oncology (DGHO). *Ann Oncol*. 2018;29(6):1354–1365. doi:10.1093/annonc/mdy117
2. Orhan B, Özkalemkaş F, Özkocaman V, et al. The role of white blood cell count in perianal pathologies: a retrospective analysis of hematologic malignancies. *Mediterr J Hematol Infect Dis*. 2022;14(1):e2022051. doi:10.4084/mjhid.2022.051
3. Solmaz S, Korur A, Gereklioğlu Ç, et al. Anorectal complications during neutropenic period in patients with hematologic diseases. *Mediterr J Hematol Infect Dis*. 2016;8(1):e2016019. doi:10.4084/mjhid.2016.019
4. Nada EM, Alshoaiby AN, Alaskar AS, Khan AN. Severe anal and abdominal pain due to typhlitis in a leukemic patient. *J Pain Symptom Manage*. 2007;34(5):457–459. doi:10.1016/j.jpainsymman.2007.07.003
5. Baker B, Al-Salman M, Daoud F. Management of acute perianal sepsis in neutropenic patients with hematological malignancy. *Tech Coloproctol*. 2014;18(4):327–333. doi:10.1007/s10151-013-1082-z
6. Cohen JS, Paz IB, O'Donnell MR, Ellenhorn JD. Treatment of perianal infection following bone marrow transplantation. *Dis Colon Rectum*. 1996;39(9):981–985. doi:10.1007/bf02054685
7. Lehrnbecher T, Marshall D, Gao C, Chanock SJ. A second look at anorectal infections in cancer patients in a large cancer institute: the success of early intervention with antibiotics and surgery. *Infection*. 2002;30(5):272–276. doi:10.1007/s15010-002-2197-8
8. Liu J, Zhang Y, He W. Construction of a novel carrimycin-producing strain by using CRISPR-Cas9 and ribosome engineering techniques. *Sheng Wu Gong Cheng Xue Bao*. 2021;37(6):2116–2126. doi:10.1007/s15010-002-2197-8
9. Logan C, Koura D, Taplitz R. Updates in infection risk and management in acute leukemia. *Hematology Am Soc Hematol Educ Program*. 2020;2020(1):135–139. doi:10.1182/hematology.2020000098
10. Loureiro RV, Borges VP, Tomé AL, Bernardes CF, Silva MJ, Bettencourt MJ. Anorectal complications in patients with haematological malignancies. *Eur J Gastroenterol Hepatol*. 2018;30(7):722–726. doi:10.1097/meg.0000000000001133
11. He W, Yang C, Zhao X, Wang Y. Antimicrobial activity of bitespiramycin, a new genetically engineered macrolide. *Bioorg Med Chem Lett*. 2017;27(19):4576–4577. doi:10.1016/j.bmcl.2017.08.046
12. Ma C, Zhou H, Li J, et al. Construction of 4-isovalerylspiramycin-I-producing strain by in-frame partial deletion of 3-O-acyltransferase gene in Streptomyces spiramyceticus WSJ-1, the bitespiramycin producer. *Curr Microbiol*. 2011;62(1):16–20. doi:10.1007/s00284-010-9664-8
13. Zimmermann P, Ziesenitz VC, Curtis N, Ritz N. The immunomodulatory effects of macrolides-a systematic review of the underlying mechanisms. *Front Immunol*. 2018;9:302. doi:10.3389/fimmu.2018.00302
14. Nan C, Zhang X, Huang W, et al. Effects of carrimycin on biomarkers of inflammation and immune function in tumor patients with sepsis: a multicenter double-blind randomized controlled trial. *Pharmacol Res*. 2023;198:106991. doi:10.1016/j.phrs.2023.106991
15. Liu Z, Huang M, Hong Y, et al. Isovalerylspiramycin I suppresses non-small cell lung carcinoma growth through ROS-mediated inhibition of PI3K/AKT signaling pathway. *Int J Biol Sci*. 2022;18(9):3714–3730. doi:10.7150/ijbs.69989
16. Cui J, Zhou J, He W, et al. Targeting selenoprotein H in the nucleolus suppresses tumors and metastases by Isovalerylspiramycin I. *J Exp Clin Cancer Res*. 2022;41(1):126. doi:10.1186/s13046-022-02350-0
17. Liang SY, Zhao TC, Zhou ZH, et al. Anti-tumor effect of carrimycin on oral squamous cell carcinoma cells in vitro and in vivo. *Transl Oncol*. 2021;14(6):101074. doi:10.1016/j.tranon.2021.101074