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INFECTIOUS AND HEMATOLOGIC TOXICITIES OF CPX-351 IN ACUTE MYELOID LEUKEMIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Introduction: Acute myeloid leukemia (AML) is an aggressive hematologic malignancy characterized by clonal proliferation of myeloid precursor cells, leading to bone marrow failure and severe cytopenias. Intensive chemotherapy, traditionally the 7+3 cytarabine/daunorubicin regimen, remains the standard of care, despite significant treatment-related toxicity and increased infectious risk. CPX-351, a liposomal formulation of cytarabine/daunorubicin delivered at a fixed synergistic ratio (1:5), has demonstrated improved survival over conventional regimens in patients with therapy-related AML and AML with myelodysplasia-related changes, leading to its regulatory approval. However, despite these benefits, safety considerations remain clinically important. Prolonged myelosuppression associated with CPX-351 may delay hematopoietic recovery and increase susceptibility to infectious complications, emphasizing the need for a comprehensive safety evaluation. **Objectives:** To synthesize available evidence on infectious and hematologic adverse events in patients with AML treated with CPX-351. **Methodology:** PubMed, Embase, and the Cochrane Library were searched from database inception up to January 2026. Outcomes included infectious complications (febrile neutropenia, bacteremia and sepsis) and hematologic adverse events (prolonged neutrophil and/or platelet recovery), graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 3. A random-effects model was used to pool risk ratios (RRs), with corresponding 95% confidence intervals (CIs). Risk of bias was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool for randomized controlled trials (RCTs), and certainty of evidence was evaluated according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool. **Results:** Four RCTs were included, comprising a total of 749 patients. Of these, 424 patients received CPX-351, while the remaining were assigned to standard chemotherapy regimens. Two studies were phase II trials, and two were phase III trials. Pooled analysis showed that CPX-351 was not associated with a higher risk of infectious-related events, with no significant differences in the incidence of febrile neutropenia (RR 1.17, 95% CI 0.89–1.54), bacteremia (RR 1.07, 95% CI 0.65–1.75) or sepsis (RR 0.99, 95% CI 0.61–1.59). Hematologic outcomes, namely neutrophil and platelet recovery, could not be pooled, but suggested a trend towards delayed hematopoietic recovery in the CPX-351 arm. Neutrophil recovery was consistently delayed with CPX-351 across all four studies (37 vs. 28 days; 36 vs. 32 days; 42 vs. 34 days; and 32 vs. 30 days).

Similarly, platelet recovery occurred later with CPX-351 (36 vs. 32 days; 37 vs. 28; 45 vs. 35 days; and 34 vs. 29 days). In the risk of bias evaluation, one study was judged to be at low risk of bias, while three studies were assessed as having some concerns. GRADE assessment rated the certainty of evidence as low to very low, primarily due to differences in study populations and the limited number of studies, which represent key limitations of this review. **Conclusions:** Overall, CPX-351 was not associated with an increased risk of infectious complications compared to standard chemotherapy; however, it may be associated with a delayed hematopoietic recovery. These findings highlight the importance of vigilant supportive care and further real-world data to better characterize its hematologic safety profile.

Keywords: CPX-351, Acute myeloid leukemia, Infections, Cytopenias, Meta-analysis.

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PROSPECTS FOR THE PRODUCTION OF THERAPEUTIC RADIOISOTOPES BASED ON INSTALLED CAPACITY IN ARGENTINA AND BRAZIL

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Therapeutic radioisotopes were first used in clinical practice in 1941 to treat thyroid cancer, using a mixture of ¹³¹I/¹³³I produced in a cyclotron. Nowadays, high-purity ¹³¹I is still used to treat thyroid disease, but it is produced in nuclear reactors. From the 1980s to the 2010s, new radioisotopes were introduced for cancer treatment, including beta (β) emitter ⁹⁰Y, ¹⁵³Sm, and ¹⁶⁶Ho. By the end of 2010, ¹⁷⁷Lu emerged as a promising radioisotope for theranostic applications, and by 2020, ¹⁶¹Tb was identified as a promising new radioisotope due to its simultaneous β and Auger-electron emission. Also, the alpha emitters ²¹¹At, ²²⁵Ac, ²¹²Pb, and ²¹³Bi have proven

effective in cancer treatment. **Requirements for radioisotopes production:** The production of these radioisotopes depends on specific nuclear reactions requiring either high-energy charged particles or high neutron fluxes. For ^{225}Ac , several methods were tested, one of the oldest is $^{232}\text{Th}(p,x)^{225}\text{Ac}$, >100 MeV. However, this route is controversial because it co-produces ^{227}Ac , a long half-life (21.7 y) alpha emitter, that makes impossible its uses in humans; alternatively $^{226}\text{Ra}(p,2n)^{225}\text{Ac} \geq 30$ MeV; other possibility is $^{226}\text{Ra}(g,n)^{225}\text{Ra}(\beta)^{225}\text{Ac}$ has been in use to produce ^{225}Ac with the higher radionuclide purity, $^{209}\text{Bi}(\alpha,2n)^{211}\text{At}$, but with alpha particles not higher than 29-28 MeV to avoid production to ^{211}Po , $^{151}\text{Eu}(^3\text{He},5n)^{149}\text{Tb}$ 40-70 MeV. Beyond the production of standard beta-emitting radioisotopes, current research focuses on the $^{160}\text{Gd}(n,\gamma)^{161}\text{Gd}(\beta)^{161}\text{Tb}$ (thermal neutron flux, in the range of 10^{13} to 10^{14} n.cm $^{-2}$.s $^{-1}$). **Reactor and cyclotron production capability in Argentina and Brazil:** Argentina and Brazil have installed 10 research reactors, but only three of them, RA-3 (10 MW, neutron $1\text{--}1.4 \times 10^{14}$) and RA-10 (30 MW, $1.4\text{--}2.5 \times 10^{14}$ (expected to be critical in 2027), by CNEA, in Argentina, and the IEA-R1 (4.5 MW, 1×10^{14}) in Brazil have the capacity to produce of therapeutic radioisotopes in commercial scale. From these, Ra-3 is producing ^{99}Mo , ^{51}Cr , ^{131}I and ^{177}Lu , and ^{161}Tb under R&D production. Currently, the IEA-R1 is not producing radioisotopes, but it is planned to return to the production of ^{131}I and start the ^{177}Lu production in 2026. Furthermore, Brazil has begun construction of the Brazilian Multipurpose Reactor (RMB), which will operate at 30 MW and is scheduled to begin

operations in 2032. There are 26 cyclotrons installed in the region, but a limited number can operate above 20 MeV, restricting the production of advanced therapeutic radionuclides. Argentina has the CP-42 (42 MeV), which is in maintenance and returning at the end of 2026, and a new center is planned to operate a 30 MeV Cyclotron in 2029, focusing on ^{225}Ac production for industrial applications. In Brazil, the IPEN is investing in cyclotron-based production of ^{225}Ac via the $^{225}\text{Ra}(p,2n)^{225}\text{Ac}$ using its 30 MeV cyclotron. In parallel, IPEN has established partnerships with multinational companies to process and purify ^{226}Ra , supporting a sustainable and scalable ^{225}Ac supply chain. **Conclusion:** The production and distribution of emerging therapeutic radioisotopes require substantial and specialized human resources, which constrain access in the region. The commissioning of new reactors, particularly RA-10 and the RMB, is expected to significantly enhance regional capabilities, while cyclotron-based production remains largely restricted to conventional medical radionuclides.

Keywords: Radioisotopes production, nuclear reactor, Cyclotron, Theranostic, Cancer.

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