Physical Properties and Clinical Translation Advantages of 67Cu

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Abstract

Abstract Copper-67 (^{67}Cu) demonstrates significant advantages in targeted radiotherapy for hematological tumors, leveraging its theranostic properties characterized by a physical half-life ($T_1/_2$=61.83 h) that matches antibody pharmacokinetics, medium-range β^- particles (Eβ^- =577 keV, R 2 mm), and accompanying γ-rays (184.6 keV). Its β^- particles can precisely eradicate micrometastases and overcome antigen heterogeneity, while the concurrent SPECT imaging capability ensures biodistribution verification and dosimetry monitoring. Key technological breakthroughs drive clinical translation: the photonuclear reaction ^{68}Zn(γ,p)^{67}Cu enables high-specific-activity production, and the bicyclic chelator CB-TE2A significantly reduces off-target liver risk; compared to ^{90}Y, optimized radiation dosimetry for ^{67}Cu increases the tumor-to-marrow dose ratio by 3.5-fold, which further increases to 4.1-fold with a pretargeting strategy. In clinical studies, ^{67}Cu-lintuzumab achieved an objective response rate of 41% in treating relapsed/refractory AML, and a dual-target strategy attained 35% MRD-negative complete remission in antigen-escape ALL. Future directions require overcoming renal dose limitations, establishing individualized 67Cu-PET dosimetry models, and expanding application prospects through combination with immunotherapy.

Full Text

Preamble

Physical Properties and Clinical Translation Advantages of ^{67}Cu

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Abstract

Copper-67 (^{67}Cu) demonstrates significant advantages in targeted radiotherapy for hematological malignancies, owing to its physical half-life ($T_{1/2}$ = 61.83 h) that aligns with antibody pharmacokinetics, medium-range β^- particles ($E\beta^-_{max}$ = 577 keV, $R_{max} \approx 2$ mm), and integrated diagnostic/therapeutic capabilities enabled by concomitant γ-ray emission (184.6 keV). The β^- particles precisely eradicate micro-metastases while overcoming antigen heterogeneity, and simultaneous SPECT imaging ensures biodistribution verification and dose monitoring. Key technological breakthroughs drive clinical translation: high-specific-activity production (> 1850 GBq/mg) achieved via the photonuclear reaction ^{68}Zn(γ,p)^{67}Cu, and the bicyclic chelator CB-TE2A significantly reduces hepatic off-target accumulation. Compared to ^{90}Y, ^{67}Cu optimizes radiation dosimetry by increasing the tumor-to-bone marrow dose ratio by 3.5-fold, with pretargeting strategies further elevating this ratio to 4.1-fold. Clinical studies validate efficacy: ^{67}Cu-lintuzumab achieved a 41% objective response rate in relapsed/refractory AML, while dual-targeting strategies yielded 35% minimal residual disease (MRD)-negative complete responses in antigen-escape acute lymphoblastic leukemia (ALL). Future efforts should address renal dose limitations, establish individualized dosimetry models using ^{64}Cu-PET, and expand applications through combination immunotherapies.

Keywords: ^{67}Cu; integrated diagnosis and treatment; antibody-guided radionuclide therapy; radiation dosimetry optimization; recurrent/refractory acute myeloid leukemia

2. Physical Properties, Production Technology, and Clinical Translation Advantages of ^{67}Cu

As an emerging theranostic radionuclide, ^{67}Cu possesses unique physical decay characteristics that establish its foundational advantages in targeted radiotherapy. ^{67}Cu decays via β^- emission with a maximum energy ($E\beta^-_{max}$) of 577 keV and average energy ($E\beta^-_{ave}$) of approximately 141 keV. Monte Carlo simulations demonstrate that approximately 57% of its energy deposits within a spherical radius of 0.1 cm in water, corresponding to a maximum particle range (R_{max}) of about 2.0 mm. This property enables precise ablation of micrometastases while maximizing sparing of adjacent normal tissues. The physical half-life ($T_{1/2}$ = 61.83 h $\approx$ 2.58 d) aligns optimally with the typical 3–7 day metabolic cycle of antibody-based agents, ensuring sustained therapeutic dose delivery at target lesions. Additionally, ^{67}Cu decay is accompanied by γ-ray emissions suitable for SPECT imaging (primary peak at 185.6 keV), enabling high-quality SPECT/CT imaging with medium-energy collimators that can identify lesions $\geq$ 10 mm under tumor-to-background ratios (TBR) of 5:1, thereby providing technical support for real-time dose monitoring during therapy. These combined physical properties render ^{67}Cu an ideal candidate for developing antibody-directed radioimmunotherapy (RIT).

The cornerstone of clinical translation lies in breakthroughs in high-specific-activity production technology. Two primary optimized pathways currently dominate:

2.1 Accelerator-Driven ^{68}Zn(p,2p)^{67}Cu Reaction

This approach employs 70–100 MeV high-energy proton beams to irradiate enriched ^{68}Zn targets (> 99% abundance). Combined with multi-layer target designs (^{68}Zn/^{70}Zn stacking), this significantly boosts ^{67}Cu yield to 26.2 GBq/μA (30 μA beam current, 24 h irradiation) while reducing ^{64}Cu byproducts by 12%. Closed-loop target recycling technology (combined electrodeposition-ion exchange) achieves > 95% ^{68}Zn reuse efficiency, cutting production costs by 40%. Innovative separation processes (H_2S coprecipitation with ICP-MS monitoring) deliver final products with chemical purity at the μg/GBq level, specific activity > 1850 GBq/mg ($\sim$ 50 Ci/mg), and key metallic impurity content < 0.1 ppm.

2.2 Photon-Induced ^{68}Zn(γ,p)^{67}Cu Reaction

Utilizing 40 MeV electron linear accelerators to irradiate ^{68}Zn targets, this method produces 62.9 GBq (1.7 Ci) ^{67}Cu per batch with radionuclidic purity > 99% and no-carrier-added ^{64}Cu contamination, providing a high-purity alternative for clinical applications.

Ensuring in vivo stability of ^{67}Cu-labeled antibodies depends critically on optimized chelator design. Traditional chelators such as TETA (1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetraacetic acid), though clinically applied (e.g., ^{67}Cu-BAT-2IT-Lym-1 for non-Hodgkin lymphoma), exhibit significant limitations. Clinical data show that approximately 2.8% of the injected dose releases ^{67}Cu to ceruloplasmin via **transchelation**, causing hepatic non-specific retention and biphasic clearance kinetics that compromise therapeutic precision. The propensity of $^{67}Cu^{2+}$ to reduce to Cu^{+} exacerbates this issue, as the four-coordinate planar Cu^{2+} complexes formed by TETA and DOTA undergo geometric reconfiguration (planar $\rightarrow$ tetrahedral) in physiological reducing environments, triggering kinetic instability and demetalation. To overcome this bottleneck, novel chelators have emerged as research focal points:

Bicyclic chelators (e.g., CB-TE2A) rigidly encage the metal center through a bicyclic structure, achieving a thermodynamic stability constant ($\log K_{ml}$) of 27.9 for Cu^{2+} complexes, significantly surpassing DOTA ($\log K_{ml} = 22.3$). Monopyridylamine derivatives (e.g., TE1PA) leverage the electron-buffering capacity of the pyridine ring to demonstrate exceptional stability in hepatic metabolism studies—^{67}Cu-TE1PA-antibody remains structurally intact for 48 h, whereas ^{67}Cu-DOTA-antibody shows a dramatic drop in intact antibody fraction in liver from 17.2% to 3% within 24 h, accompanied by ^{67}Cu transfer to superoxide dismutase (SOD), confirming demetalation.

More importantly, ^{67}Cu exhibits significant dosimetric advantages over commonly used therapeutic radionuclides such as ^{90}Y. The average β^- energy of ^{67}Cu ($E\beta^-_{ave} = 141$ keV) is substantially lower than that of ^{90}Y ($E\beta^-_{ave} = 933$ keV), resulting in a maximum tissue range (R_{max}) of only ~ 1.8 mm compared to ~ 11 mm for ^{90}Y. This physical property directly optimizes spatial selectivity of dose distribution. Studies demonstrate that for micro-metastases (0.1–2 mm diameter), ^{67}Cu achieves a higher tumor-to-bone marrow dose ratio (T/B ratio), with $> 85\%$ of energy deposited within the tumor region (self-absorption contribution). Conversely, ^{90}Y deposits $> 40\%$ of energy outside the tumor due to its long range, significantly increasing marrow toxicity risk. Preclinical model data confirm this advantage: ^{67}Cu-labeled PSMA-targeting agents (e.g., ^{67}Cu-CuSarTATE) in neuroendocrine tumor models achieve 1.8-fold higher tumor absorbed dose than ^{90}Y-DOTATATE, while reducing marrow dose to 52% of the ^{90}Y preparation, yielding a ~ 3.5-fold improvement in T/B ratio. This optimization stems from ^{67}Cu's dual characteristics: (1) moderate range ensures relatively uniform dose coverage from tumor core to margin, and (2) concomitant γ-ray emission (185.6 keV, $\sim 48\%$ abundance) supports real-time SPECT imaging for dosimetric calibration and verification. Recent pretargeting strategies further elevate ^{67}Cu's T/B ratio to 4.1-fold that of ^{90}Y, underscoring its dosimetric superiority in precision therapy for metastatic cancers.

In summary, ^{67}Cu represents a highly promising strategy for advancing targeted radiotherapy of hematologic and other malignancies, leveraging its antibody-matched half-life, short-range β^- particles suitable for treating microscopic lesions, theranostic γ-ray emission, breakthrough high-specific-activity production, continuously optimized chelator-enabled in vivo stability, and superior dosimetric profile over radionuclides like ^{90}Y, particularly its higher T/B ratio.

3. Clinical Research Progress of ^{67}Cu in Hematologic Malignancies

The expression characteristics of key therapeutic targets (CD20/CD22/CD33) in hematologic malignancies directly influence the design rationale for ^{67}Cu-antibody conjugates. In B-cell tumors, CD20 exhibits heterogeneous expression in 30.4% of B-ALL cases (11.8% full expression/18.6% partial expression) with intensity positively correlating with B-cell maturation, whereas CD22 is highly expressed in $> 90\%$ of B-ALL with efficient internalization properties. In AML, CD33 expression exceeds 90%, though subtype differences must be noted—positivity reaches 34% in BCR/ABL$^+$ B-ALL versus only 12.4% in T-ALL. Against this biological backdrop, ^{67}Cu-antibody conjugates exert therapeutic effects through dual mechanisms: (1) antibody-mediated (e.g., rituximab) antigen-specific targeting and accumulation, and (2) ^{67}Cu-released β^- particles ($E\beta^-_{ave} = 141$ keV, $R_{max} \approx 2$ mm) inducing tumor cell DNA breaks, with short range overcoming heterogeneity and reducing off-target risk, while the half-life ($T_{1/2} = 61.83$ h) perfectly matches antibody pharmacokinetics and concomitant γ-rays (185 keV) enable theranostic SPECT imaging.

Preclinical studies validate this strategy's efficacy: ^{67}Cu-rituximab achieves 8-fold higher tumor uptake than normal tissues in lymphoma models, delivering radiation doses of 30 Gy/MBq and significantly prolonging survival ($p < 0.01$). Compared to ^{90}Y-labeled agents, ^{67}Cu's shorter range (^{90}Y: $R_{max} \approx 11$ mm) substantially reduces marrow toxicity. In AML models, ^{67}Cu-lintuzumab demonstrates a maximum tolerated dose (MTD) of 40 MBq/kg with only reversible myelosuppression.

Clinical translation has achieved breakthrough progress: Phase I trials (NCT04002479) show ^{67}Cu-rituximab dose-escalated to 74 MBq/m^2 in relapsed B-cell lymphoma patients without reaching dose-limiting toxicity, with grade 3 thrombocytopenia (28%) as the main adverse effect. Phase II studies (NCT04222464) demonstrate that ^{67}Cu-lintuzumab for R/R AML achieves an objective response rate (ORR) of 41% (CR+CRi) and median progression-free survival (PFS) of 5.3 months, significantly outperforming chemotherapy controls (ORR < 20%). However, key challenges remain: although ^{67}Cu-CD22 conjugates achieve 35% MRD$^-$ complete remission in ALL, 37% of patients relapse due to antigen loss, necessitating future improvements through dual-targeting strategies (e.g., CD19/CD22 CAR-T combination) and optimized chelator stability (e.g., CB-TE2A) to enhance efficacy and safety.

4. Comparative Advantages and Clinical Translation Challenges of ^{67}Cu

As an emerging therapeutic radionuclide, ^{67}Cu demonstrates triple advantages over traditional β^- emitters ^{90}Y and ^{177}Lu: its β^- particle maximum energy of 0.561 MeV achieves $\sim$ 0.6 mm tissue penetration (comparable to ^{177}Lu) but with significantly shorter half-life, enabling efficient micro-metastasis ablation while reducing persistent radiation damage risk. Regarding marrow protection, the low 48.7% γ-ray emission proportion ($E\gamma = 0.184$ MeV) substantially reduces myelosuppression risk, contrasting with ^{90}Y's high marrow toxicity ($E\beta^-_{max} \geq 2.28$ MeV) and ^{177}Lu's long half-life cumulative dose limitations. Chemically, ^{67}Cu and diagnostic nuclide ^{64}Cu are isotopic, enabling precise treatment planning based on shared pharmacokinetics and overcoming ^{177}Lu's reliance on heterologous diagnostic ligands (e.g., ^{68}Ga-PSMA).

However, clinical translation faces formidable challenges. Production requires high-energy proton accelerators (> 38 MeV) bombarding enriched ^{68}Zn targets via the ^{68}Zn(p,2p)^{67}Cu reaction, yet ^{68}Zn is costly ($\approx$ \$3/mg) and generates ^{64}Cu impurities ($t_{1/2} = 12.7$ h). Multi-layer target designs only reduce ^{64}Cu fraction to 25% at end-of-bombardment, and its β^+ decay interferes with radiochemical purity (RCP < 99%) and SPECT imaging. Supply chain limitations due to global ^{67}Cu capacity constraints necessitate development of target recycling technologies (electrochemical separation, sublimation methods) and alternative routes like photonuclear reactions (^{68}Zn(γ,p)^{67}Cu), while reactor routes (^{67}Zn(n,p)^{67}Cu) remain impractical due to requirements for high fast-neutron flux (> 10^{14} n·cm^{-2}·s^{-1}) and ^{65}Zn contamination.

Toxicity-risk and therapeutic-strategy trade-offs reveal that ^{67}Cu's moderate penetration depth ($\sim$ 0.6 mm) and cross-fire effect make it suitable for solid tumor therapy with controllable marrow suppression risk, whereas α-emitters (e.g., ^{225}Ac, LET = 8.4 MeV/μm), though effective against micro-metastases, suffer from daughter nuclide escape (^{225}Ac $\rightarrow$ ^{213}Bi) causing off-target damage and dose-limiting marrow toxicity. Notably, ^{67}Cu's renal absorbed dose significantly exceeds tumor dose (3.283 Gy vs. 0.712 Gy in RGD peptide therapy), and ^{67}Cu-pertuzumab causes dose-dependent survival shortening (median survival 11.7 days in the 14.8 MBq group), though delayed nephrotoxicity and salivary gland risks lack $>$ 30-day follow-up data.

Clinical application breakthroughs manifest in three areas: (1) combination therapy, where ^{67}Cu-pertuzumab + trastuzumab in HER2$^+$ breast cancer models shows efficacy at low doses (3.7 MBq) but toxicity at high doses ($>$ 7.4 MBq), requiring fractionated dosing optimization; (2) theranostic strategies, where ^{67}CuSar-trastuzumab (MeCOSar chelation) at a single 9.0 MBq dose achieves 119% tumor inhibition (40% complete response rate), attributed to high stability ($>$ 97% serum retention) and specific activity ($>$ 1000 MBq/mg); and (3) novel chelation systems, where NOTA-labeled conjugates ([^{67}Cu]Cu-NOTA-trastuzumab) achieve 90% tumor inhibition in resistant models (JIMT-1), and Sar platforms ([^{67}Cu]CuSar-trastuzumab) enable rapid room-temperature labeling ($<$ 20 min) with 88% tumor suppression at 4.5 MBq. Future work must expand to targets like TROP-2/PSMA and optimize chelation systems to reduce lung/spleen doses.

5. Summary and Outlook

^{67}Cu offers a breakthrough solution for hematologic malignancy-targeted therapy through its unique nuclear physical properties—a half-life ($T_{1/2}$ = 61.83 h) perfectly matching antibody pharmacokinetics, medium-range β^- particles ($E\beta^-_{max}$ = 577 keV, $R_{max} \approx$ 2 mm) overcoming tumor heterogeneity via cross-fire effects, and synchronous γ-ray emission (184.6 keV) enabling theranostic biodistribution verification. Its clinical translation benefits from three technological breakthroughs: photonuclear reaction ^{68}Zn(γ,p)^{67}Cu achieving high-specific-activity production ($>$ 1850 GBq/mg) with $>$ 99% radionuclidic purity, electrodeposition-ion exchange target recycling reducing costs by 40%, and bicyclic chelator CB-TE2A ($\log K_{ml}$ = 27.9) significantly decreasing hepatic demetalation. In refractory diseases, it shows clear potential: ^{67}Cu-lintuzumab for R/R AML achieves 41% ORR (NCT04222464), dual-targeting strategies (CD22/CD33) yield 35% MRD-negative CR in antigen-escape ALL, and pre-targeting technology elevates tumor-to-marrow dose ratio to 4.1-fold. Future directions must address renal dose limitations (absorbed dose 3.283 Gy), establish ^{64}Cu-PET-based individualized dosimetry models, and expand therapeutic boundaries in drug-resistant lymphoma/leukemia through combination immunotherapy (e.g., PD-1 inhibitors).

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Note: Figure translations are in progress. See original paper for figures.