Physical Properties and Clinical Translation Advantages of 67Cu

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Date: 2025-07-02T08:30:45+00:00

Abstract

Copper-67 (Cu) exhibits significant advantages in targeted radiotherapy for hematological tumors, owing to its theranostic characteristics that include a physical half-life (T / =61.83 h) well-suited to antibody pharmacokinetics, medium-range particles (E =577 keV, R 2 mm), and accompanying -ray emission (184.6 keV). Its particles can precisely eradicate micrometastases and overcome antigen heterogeneity, while concurrent SPECT imaging capability enables biodistribution verification and dosimetry monitoring. Key technological breakthroughs driving clinical translation include: photonuclear reaction Zn(,p) Cu achieving high specific activity production (>1850 GBq/mg), and bicyclic chelator CB-TE2A (logK=27.9) significantly reducing off-target liver risk; compared to Y, radiopharmaceutical dosimetry optimization with Cu enhances the tumor/bone marrow dose ratio by 3.5-fold, which further increases to 4.1-fold with pretargeting strategies. In clinical studies, Cu-lintuzumab treatment for relapsed/refractory AML achieved an objective response rate of 41% (NCT04222464), while dual-target strategies attained 35% MRD-negative complete remission in antigen-escape ALL. Future developments must address renal dose limitations, establish individualized dosimetry models using Cu-PET, and expand therapeutic prospects through combination immunotherapy.

Full Text

Physical Properties and Clinical Translation Advantages of Cu

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Abstract

Copper-67 (Cu) demonstrates significant advantages in targeted radiotherapy for hematological malignancies, owing to its physical half-life (T / = 61.83 h) that aligns with antibody pharmacokinetics, medium-range particles (E = 577 keV, R 2 mm), and integrated diagnostic/therapeutic capabilities enabled by concomitant -ray emission (184.6 keV). The 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 Zn(,p) Cu, and the bicyclic chelator CB-TE2A (logK = 27.9) significantly reduces hepatic off-target accumulation. Compared to Y, 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 its efficacy: Cu-lintuzumab achieved a 41% objective response rate in relapsed/refractory AML (NCT04222464), 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 Cu-PET, and expand applications through combination immunotherapies.

Key words: Cu; Integrated diagnosis and treatment; Antibody guided radionuclide therapy; Radiation dosimetry optimization; Recurrent/refractory acute myeloid leukemia

1. Therapeutic Evolution and the Emergence of Cu

Treatment strategies for hematological malignancies have shifted from conventional chemotherapy toward targeted and immunotherapeutic approaches, yet clinical translation remains constrained by drug resistance and inadequate targeting precision. Major challenges include: targeted drug resistance driven by tumor genomic heterogeneity and dynamic evolution (e.g., BCR-ABL inhibitors failing in chronic myeloid leukemia due to T315I mutations); CAR-T cell therapy breakthroughs in B-cell malignancies tempered by relapse in 30–50% of patients from antigen escape or T-cell exhaustion; monoclonal antibody efficacy limited by ADCC resistance mediated by complement regulatory protein overexpression in the tumor microenvironment; and novel bispecific antibodies and antibody-drug conjugates (ADCs) that, despite improved efficacy, frequently cause significant hematological toxicity from off-target effects [1][2][3][4][5]. Consequently, overcoming tumor heterogeneity, enhancing targeting precision, and maintaining durable immune effects represent urgent unmet needs.

In this context, radionuclide therapy (RNT) offers a novel pathway to circumvent these bottlenecks through its capacity to kill antigen-heterogeneous cells and exploit physical cascade effects. Copper-67 (Cu) has re-emerged as a particularly promising agent, reshaping the theranostics landscape. Its physical

half-life (T / = 61.8 h) closely matches the pharmacokinetics of antibody-based drugs (4–7 days for target accumulation), enabling higher tumor uptake compared to shorter-lived nuclides like Y (T / = 2.67 d) while reducing myelotoxicity risk versus longer-lived nuclides such as ¹ Lu (T / = 6.65 d) [6][7][8]. Cu delivers therapeutic effects through medium-energy decay (E , = 577 keV, E , 141 keV) while simultaneously emitting -rays suitable for SPECT imaging (91.3, 93.3, 184.6 keV), achieving "single-nuclide theranostics" with consistent biodistribution and avoiding dosimetric biases from heterologous nuclide pairs (e.g., Ga/¹ Lu) that arise from chelator affinity differences [9][10].

Recent technological advances have further propelled Cu applications: High-energy photon-induced reactions Zn(,p) Cu have elevated specific activity to >1850 GBq/mg, ensuring clinical-grade supply, while highly stable chelator development has optimized radiolabeling efficiency and in vivo stability [11]. Building on these foundations, Cu-labeled antibody conjugates have demonstrated high tumor retention and manageable toxicity in preclinical studies of relapsed/refractory lymphoma and multiple myeloma [12][13]. Collectively, Cu' s matched pharmacokinetic properties, ideal nuclear physical characteristics, and production technological advances offer a highly promising strategy to overcome targeted therapy dilemmas in hematological malignancies and create new opportunities for precision radioimmunotherapy.

2. Physical Properties, Production Technology, and Clinical Advantages of Cu

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As an emerging theranostic radionuclide, Cu' s unique physical decay characteristics establish its foundational advantages in targeted radiotherapy. Cu decays via emission with a maximum energy (E ,) of 577 keV and average energy (E ,) of approximately 141 keV. Monte Carlo simulations demonstrate that approximately 57% of its energy deposits within a 0.1 cm spherical radius in water, corresponding to a maximum particle range (R) of about 2.0 mm. This property enables precise eradication of micro-metastases while maximizing sparing of adjacent normal tissues [15]. The physical half-life (T / = 61.83 h 2.58 d) closely matches the typical 3–7 day metabolic cycle of antibody-based drugs (e.g., monoclonal antibodies), ensuring sustained therapeutic dose delivery to target lesions. Additionally, Cu decay is accompanied by -ray emission suitable for SPECT imaging (primary peak at 185.6 keV), enabling high-quality SPECT/CT imaging with medium-energy collimators to identify lesions 10 mm under tumor-to-background ratios (TBR) of 5:1, while providing technical support for real-time dose monitoring during therapy [14][15]. These combined phys-

ical properties render Cu an ideal candidate for developing antibody-directed radionuclide therapy (RIT).

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

2.1 Accelerator-Driven Zn(p,2p) Cu Reaction

This approach employs 70–100 MeV high-energy proton beams to irradiate enriched Zn targets (>99% abundance). Combined with multi-layer target designs (Zn/ Zn stacking), this significantly boosts Cu yield to 26.2 GBq/ A (30 A beam current, 24-hour irradiation) while reducing Cu byproducts by 12% [16]. Closed-loop target recycling technology (combined electrodeposition-ion exchange) achieves >95% Zn reuse efficiency, cutting production costs by 40% [17]. Innovative separation processes (H S coprecipitation with ICP-MS monitoring) achieve final product chemical purity at g/GBq levels, specific activity >1850 GBq/mg (~50 Ci/mg), and key metal impurity content <0.1 ppm [18][19].

2.2 Photon-Induced Zn(,p) Cu Reaction

Utilizing 40 MeV electron linear accelerators to irradiate Zn targets, this method yields 62.9 GBq (1.7 Ci) Cu per batch with >99% radionuclidic purity and no carrier-added Cu contamination, providing a high-purity alternative for clinical applications [20].

Ensuring in vivo stability of Cu-labeled antibodies hinges on optimized chelator design. Traditional chelators like TETA (1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetraacetic acid), though clinically applied (e.g., Cu-BAT-2IT-Lym-1 for non-Hodgkin lymphoma), exhibit significant limitations [21]. Clinical data show approximately 2.8% of injected dose releases Cu to ceruloplasmin through transchelation, causing hepatic non-specific retention and biphasic clearance kinetics that compromise therapeutic precision [22]. Cu² ' s propensity to reduce to Cu exacerbates this issue, as TETA and DOTA form four-coordinate planar Cu² complexes prone to geometric reconfiguration (planar→tetrahedral) in physiological reducing environments, triggering kinetic instability and demetalation [22][23]. Novel chelators have emerged to overcome this bottleneck:

Bicyclic Chelators (e.g., CB-TE2A): These rigid bicyclic structures firmly lock the metal center, achieving a thermodynamic stability constant (log K) of 27.9 for Cu² complexes, significantly surpassing DOTA (log K = 22.3) [24].

Mono-Pyridine Amine Derivatives (e.g., TE1PA): Leveraging the electron-buffering capacity of the pyridine ring, these demonstrate exceptional stability in hepatic metabolism studies– Cu-TE1PA-antibody remained structurally intact for 48 hours, whereas Cu-DOTA-antibody showed hepatic intact antibody proportion plummeting from 17.2% to 3% within 24 hours,

accompanied by Cu transfer to superoxide dismutase (SOD), confirming demetalation [25].

Critically, Cu exhibits significant dosimetric advantages over conventional therapeutic nuclides like Y. Cu' s average energy (E , = 141 keV) is substantially lower than Y' s (E , = 933 keV), yielding a maximum tissue range (R) of only ~1.8 mm versus ~11 mm for Y. This property directly optimizes spatial selectivity in dose distribution. Studies show that for micrometastases (0.1–2 mm diameter), Cu achieves higher tumor-to-bone marrow dose ratios (T/B ratio), with >85% of energy deposited within tumor regions (self-absorption contribution). Conversely, Y' s long range causes >40% energy deposition outside tumors, significantly increasing myelotoxicity risk [26][27][28]. Preclinical models confirm this advantage: Cu-labeled PSMA-targeted agents (e.g., Cu-CuSarTATE) delivered 1.8-fold higher tumor absorbed dose than Y-DOTATATE in neuroendocrine tumor models, while reducing bone marrow dose to 52% of Y preparations, yielding a ~3.5-fold T/B ratio improvement [29]. This optimization stems from Cu' s dual characteristics: (1) moderate range ensures relatively uniform dose coverage from tumor core to periphery, and (2) concomitant -ray emission (185.6 keV, ~48% abundance) supports real-time SPECT imaging for dosimetric calibration and verification [30]. Advanced pretargeting strategies have further elevated Cu' s T/B ratio to 4.1-fold that of Y, underscoring its dosimetric superiority in metastatic cancer precision therapy [31].

In summary, Cu' s matched antibody pharmacokinetic half-life, short-range particles ideal for treating microscopic lesions, theranostic -ray emission, breakthrough high-specific-activity production, evolving chelator-enabled in vivo stability, and superior dosimetric properties over nuclides like Y (particularly higher T/B ratios) collectively establish it as a highly promising strategy for advancing targeted radiotherapy in hematological and other malignancies.

3. Clinical Research Progress of Cu in Hematological Malignancies

Expression profiles of key therapeutic targets (CD20/CD22/CD33) directly influence the design rationale for Cu-antibody conjugates. In B-cell tumors, CD20 shows heterogeneous expression in 30.4% of B-ALL cases (11.8% full expression/18.6% partial expression) with intensity correlating positively with B-cell maturity, while CD22 is highly expressed in >90% of B-ALL with efficient internalization characteristics. In AML, CD33 expression exceeds 90%, though subtype differences warrant attention—positivity reaches 34% in BCR/ABL B-ALL versus only 12.4% in T-ALL [32][43]. Against this biological backdrop, Cu-antibody conjugates exert therapeutic effects through dual mechanisms: (1) antibody-mediated (e.g., rituximab) antigen-specific target accumulation, and (2) Cu-released particles (E , = 141 keV, R 2 mm) inducing tumor cell DNA breaks, with short range overcoming heterogeneity and reducing off-target risk. The half-life (T / = 61.83 h) perfectly matches antibody pharmacokinet-

ics, while accompanying -rays (185 keV) enable theranostic SPECT imaging [40][Error! Reference source not found.][41][42].

Preclinical studies validate this strategy's effectiveness: Cu-rituximab achieved 8-fold higher tumor uptake than normal tissues in lymphoma models, delivering 30 Gy/MBq radiation dose and significantly prolonging survival ($p < 0.01$) [45]; compared to Y-labeled drugs, Cu' s shorter range (Y: R 11 mm) substantially reduced myelotoxicity [46]; in AML models, Cu-lintuzumab maximum tolerated dose (MTD) was 40 MBq/kg with only reversible myelosuppression observed [47].

Clinical translation has achieved breakthrough progress: Phase I trial (NCT04002479) demonstrated Cu-rituximab dose escalation to 74 MBq/m² in relapsed B-cell lymphoma patients without reaching dose-limiting toxicity, with grade 3 thrombocytopenia (28%) as the main adverse effect [48]. Phase II study (NCT04222464) showed Cu-lintuzumab achieved 41% objective response rate (ORR) (CR+CRi) in R/R AML with median progression-free survival (PFS) of 5.3 months, significantly outperforming chemotherapy controls (ORR < 20%) [51]. However, key challenges persist: Cu-CD22 conjugates achieved 35% MRD-negative complete response rate in ALL, yet 37% of patients relapsed due to antigen loss, necessitating future dual-target strategies (e.g., CD19/CD22 CAR-T combination [36]) and chelator stability optimization (e.g., CB-TE2A [44]) to further improve efficacy and safety.

4. Comparative Advantages and Clinical Translation Challenges of Cu

As an emerging therapeutic radionuclide, Cu demonstrates triple advantages over traditional emitters Y and ^{1} Lu: its particle maximum energy of 0.561 MeV achieves ~0.6 mm tissue penetration (comparable to ^{1} Lu) but with significantly shorter half-life, enabling efficient micro-metastasis killing while reducing persistent radiation damage risk; myeloprotection benefits from low 48.7% -ray emission (E = 0.184 MeV) that substantially reduces myelosuppression risk, contrasting with Y' s high myelotoxicity (E , 2.28 MeV) and ^{1} Lu' s long half-life cumulative dose limitations [49][50]; chemically, Cu shares elemental identity with diagnostic nuclide Cu, enabling precise treatment planning based on shared pharmacokinetics and overcoming ^{1} Lu' s reliance on heterologous diagnostic ligands (e.g., Ga-PSMA) [49][51]. However, clinical translation faces formidable challenges: production requires high-energy proton accelerators (>38 MeV) bombarding enriched Zn targets (Zn(p,2p) Cu), yet Zn is costly (~$3/mg) and generates Cu impurities (t / = 12.7 h), with multi-layer target designs only reducing Cu fraction to 25% (at EOB), whose decay interferes with radiochemical purity (RCP < 99%) and SPECT imaging [61][22]; supply chains are constrained by insufficient global Cu capacity, necessitating target recycling technologies (electrochemical separation [59], sublimation [60]) and alternative photonuclear reactions (Zn(,p) Cu), while reactor routes (Zn(n,p) Cu) remain impractical due to required fast neutron fluxes (>10^{1} n·

cm ^{2} • s ^{1}) and Zn contamination [63][64].

Toxicity risk and therapeutic strategy trade-offs reveal: Cu' s moderate penetration depth (~0.6 mm) and crossfire effect suit solid tumor treatment with manageable myelosuppression risk [56][57]; -emitters (e.g., ^{22} Ac, LET = 8.4 MeV/ m) effectively target micro-metastases but suffer from daughter nuclide escape (^{22} Ac → ^{213}Bi) causing off-target damage and dose-limiting myelotoxicity [54][55]. Notably, Cu' s renal absorbed dose significantly exceeds tumor dose (3.283 Gy vs. 0.712 Gy in RGD peptide therapy), and Cu-pertuzumab causes dose-dependent survival shortening (median survival 11.7 days at 14.8 MBq), though delayed nephrotoxicity and salivary gland risks lack >30-day follow-up data [65][66].

Clinical breakthroughs manifest in three areas: (1) Combination therapy— Cu-pertuzumab plus trastuzumab in HER2 breast cancer models shows efficacy at low dose (3.7 MBq) but toxicity at high dose (>7.4 MBq), requiring fractionated dosing optimization [66]; (2) Theranostic strategies— CuSar-trastuzumab (MeCOSar chelation) single dose 9.0 MBq achieved 119% tumor inhibition (40% complete response rate), attributed to high stability (>97% serum retention) and specific activity (>1000 MBq/mg) [72]; (3) Novel chelation systems—NOTA conjugates ([Cu]Cu-NOTA-trastuzumab) achieved 90% tumor inhibition in resistant models (JIMT-1), while Sar platforms ([Cu]CuSar-trastuzumab) enabled rapid room-temperature labeling (<20 minutes) with 88% tumor suppression at 4.5 MBq dose [68]. Future work must expand to targets like TROP-2/PSMA and optimize chelation systems to reduce lung/spleen dose.

5. Summary and Outlook

Cu offers a breakthrough solution for hematological malignancies through unique nuclear properties: a half-life (T / = 61.83 h) perfectly matched to antibody pharmacokinetics, medium-range particles (E , = 577 keV, R 2 mm) overcoming tumor heterogeneity via crossfire effects, and simultaneous -ray emission (184.6 keV) enabling theranostic biodistribution verification. Clinical translation benefits from three technological breakthroughs: photonuclear reaction Zn(,p) 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 (logK = 27.9) significantly decreasing hepatic demetalation. Clear potential emerges in refractory diseases: Cu-lintuzumab achieved 41% ORR in R/R AML (NCT04222464), dual-target strategies (CD22/CD33) attained 35% MRD-negative CR in antigen-escape ALL, and pretargeting technology elevated tumor/bone marrow dose ratio to 4.1-fold. Future priorities include overcoming renal dose limitations (absorbed dose 3.283 Gy), establishing individualized Cu-PET dosimetry models, and expanding therapeutic frontiers in drug-resistant lymphoma/leukemia through combination immunotherapy (e.g., PD-1 inhibitors).

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