Biodistribution, Imaging and Metabolism Studies of 64-Copper Radiolabelled Monoclonal Antibody : Comparison of DOTA and TE1PA Chelating Agents in a Murine Model of Multiple Myeloma

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Purpose: TE1PA is a ***C***-functionalized monopicolinate cyclam designed for 64-copper chelation. It was proven to have excellent Cu(II) and Cu(I) chelation properties, with fast kinetics, high thermodynamic stability and resistance to transchelation ***in vitro***, and a usefulness for phenotypic imagery when coupled to antibodies. This work presents ***in vivo*** studies (biodistribution, metabolism and imaging) of TE1PA in a syngenic multiple myeloma model on mice, compared to DOTA, its main competitor. **Materials and methods:** ***p***-SCN-Bn-TE1PA and DOTA-NHS ester were grafted on 9E7.4 rat IgG_{2a} antibody, targeting murine CD-138. Immunoconjugates were then radiolabelled with ^{64}Cu. Both ^{64}Cu-9E7.4-***p***-SCN-Bn-TE1PA and ^{64}Cu-9E7.4-NHS-DOTA were injected in 12 mice previously grafted with 5T33 cells, allowing the development of subcutaneous tumors expressing CD-138. Each mouse was injected with 100 µg of radioimmunoconjugates corresponding to 10 MBq of ^{64}Cu. For each time studied (2h, 24h and 48h post-injection), a biodistribution and a liver metabolism studies were conducted on mice for both radiolabelled antibodies. Additionally, a micro-PET scan was performed on 4 mice injected with ^{64}Cu-9E7.4-***p***-SCN-Bn-TE1PA at those 3 times. **Results:** Biodistribution study shows an excellent hepatic clearance of the ^{64}Cu-9E7.4-***p***-SCN-Bn-TE1PA over time. Significantly higher radioactivity was found in blood, lungs and heart at 48h PI for ^{64}Cu-9E7.4-NHS-DOTA, which suggests a release of ^{64}Cu from antibody, in parallel with a higher intestinal elimination. This was correlated by the liver metabolism study, which shows a better ***in vivo*** resistance to transchelation for ^{64}Cu-9E7.4-***p***-SCN-Bn-TE1PA. The imaging study of ^{64}Cu-9E7.4-***p***-SCN-Bn-TE1PA shows an increasing targeting of the tumors over time and confirms the hepatic clearance at 24h and 48h PI. **Conclusion:** ^{64}Cu-9E7.4-***p***-NCS-Bn-TE1PA has shown a very high tumor targeting, associated to an increasing of tumor-to-tissues ratio over time that suggests an overall clearance from healthy tissues. Compared to DOTA, TE1PA displays an ***in vivo*** stability and resistance to transchelation significantly superior. This confirms the previous results obtained ***in vitro*** and ^{64}Cu-labelled TE1PA proved once again its usefulness for immuno-PET imaging in a preclinical model.