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Exploring Ga-68 Trastuzumab Fab for noninvasive PET imaging to detect HER2 expressing lesions.

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Background: HER 2 is a transmembrane protein expressed in variety of tissues involved in cell development, proliferation and differentiation. Amplification of HER2 gene leads to overexpression of HER2 receptors and uncontrolled growth. HER2 expression is associated with aggressiveness of tumor. The anti HER2 monoclonal antibody, Trastuzumab (145 kDa), binds to domain IV of HER2 receptor and inhibit the tumor growth. The fragment of trastuzumab bearing antigen binding site, Fab (45 kDa), is explored for imaging HER2 expression in breast cancer patients.
Methodology: The Trastuzumab Fab was generated with papain digestion and conjugated with a bifunctional chelating agent NOTA. The NOTA conjugated Ga-68 trastuzumab Fab was separated and was radiolabeled with freshly eluted Ga-68 from Ge-68/Ga-68. Radiolabeled Ga-68 NOTA- Ga-68 trastuzumab Fab (Ga-68 trastuzumab Fab) was separated using PD-10 column and passed through 0.22 µm filter for sterility. The radiochemical purity of Ga-68 Fab was assessed by paper chromatography using sodium-citrate (pH-5.5) as mobile phase, apyrogenicity with PTS and sterility in culture broth for 7 days. The patients (n=7) with immunohistochemistry (IHC) proven HER 2 expressing breast cancer (n=7) and HER 2 negative (n=2) were recruited. The F-18 FDG PET/CT was done in all patients. After obtaining permission from Institute and informed written consent from patients, Ga-68 trastuzumab Fab (3-5 mCi) was injected and PET/CT was acquired after 1.5, 3.0 hr. Scans were analyzed by two nuclear medicine physicians and compared with F-18 FDG findings.
Results and discussion: The Fab region of trastuzumab is responsible for binding with HER2 ligand binding domain. Fab was generated by papain digestion and separated by desalting (P-10 column). The NOTA conjugation was standardized at 4℃ and 22-24 hours incubation time and average 1.5 NOTA molecules per Fab (MALDI-TOF) were conjugated at 25:1 molar ratio of NOTA:Fab. The Labeling efficiency of Ga-68 trastuzumab Fab was more than 50% and after purification, the radiochemical purity was >95%. The Ga-68 trastuzumab Fab was found sterile and pyrogenic. Ga-68 trastuzumab Fab MIP PET image showed high blood pool activity at 1.5 h, which was decreased at 3 h. However, high kidney and bladder activity demonstrated clearance by renal route. The uptake at primary and metastatic lesions was visualized at 1.5 h and increased at 3 h, in terms of SUVmax, in all HER 2 expressing patients. However, no uptake was observed in HER 2 negative patients. The liver uptake was noted in all patients. The lesions detected on Ga-68 trastuzumab Fab PET/CT were comparable with F-18 FDG PET/CT. To best of our knowledge this is the first human study using Ga-68-Fab.
Conclusion

The Ga-68 Fab has been formulated and demonstrated potential for targeting HER2 positive lesions. In future, this imaging could be utilized to demonstrate the pattern of HER2 receptor throughout the body before and after trastuzumab and trastuzumab radioimmunotherapy therapy.

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