न्यूरोएंडोक्राइन ट्यूमर का पीईटी-प्रतिबिंबन

2

^{68}Ga-NODAGA-JR11 के सरल और सुविधाजनक संरूपण हेतु एकल-वॉयल किट का विकास : न्यूरोएंडोक्राइन ट्यूमर के निदान हेतु पीईटी कर्मक

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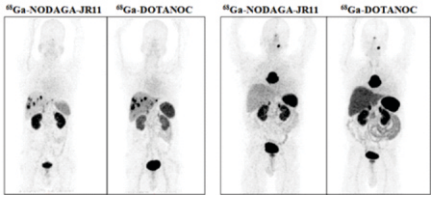

नेट रोगियों में ^{68}Ga-NODAGA-JR11 और ^{68}Ga-DOTANOC का पी. ई. टी./सीटी स्कैन

सारांश

^{68}Ga-NODAGA-JR11 न्यूरोएंडोक्राइन ट्यूमर की PET-प्रतिबिंबन के लिए एक आशाजनक सोमैटोस्टैटिन एंटागोनिस्ट के रूप में उभरा है। मानव कैंसर रोगियों में कारक की आरंभिक के सफलता पूर्ण मूल्यांकन हेतु आगे के बहु-केंद्रित नैदानिक परीक्षणों की आवश्यकता है। अस्पताल रेडियोफार्मेसी में ^{68}Ga-NODAGA-JR11 का एकल-चरण निर्माण बहु-केंद्र परीक्षणों को सुविधाजनक बनाने वाले अस्पतालों की बढ़ती भागीदारी को प्रोत्साहित करेगा। इस प्रकार, ^{68}Ga-NODAGA-JR11 के सुविधाजनक निर्माण के लिए फ्रीज-ड्राय किट विकसित किए गए और न्यूरोएंडोक्राइन कैंसर रोगियों में प्रारंभिक नैदानिक अध्ययन किए गए। सरूपित किट ^{68}Ga-NODAGA-JR11 ने प्राथमिक और साथ ही मेटास्टेटिक घावों में उच्च अवशोषण प्रदर्शित किया।

PET-imaging of Neuroendocrine Tumors

2

Development of Single-vial Kit for Simple and Convenient Formulation of ^{68}Ga-NODAGA-JR11: PET Agent for Diagnosis of Neuroendocrine Tumor

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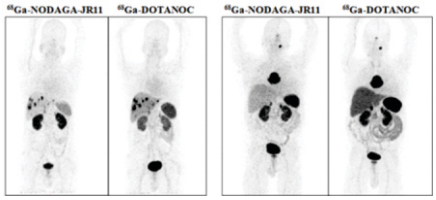

PET/CT scan of ^{68}Ga-NODAGA-JR11 and ^{68}Ga-DOTANOC in NET patients

ABSTRACT

^{68}Ga-NODAGA-JR11 has emerged as a promising somatostatin antagonist for PET-imaging of neuroendocrine tumors. Preliminary success of the agent necessitates further multi-centric clinical trials for complete evaluation in human cancer patients. Single-step formulation of ^{68}Ga-NODAGA-JR11 at hospital radiopharmacy shall encourage increased participation of hospitals facilitating multi-centre trials. Thus, freeze-dried kits were developed for convenient formulation of ^{68}Ga-NODAGA-JR11 and preliminary clinical studies were performed in neuroendocrine cancer patients. Kit formulated ^{68}Ga-NODAGA-JR11 exhibited high uptake in primary as well as metastatic lesions.

KEYWORDS: *NODAGA-JR11, Neuroendocrine tumor, Somatostatin antagonist, Freeze-dried kit, PET/CT imaging*

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Introduction

^{68}Ga-NODAGA-JR11 (^{68}Ga-OPS202), a novel radiolabeled somatostatin receptor (sstr) antagonist exhibiting high affinity towards sst_2 receptors, has emerged as a promising radiotracer for PET imaging of neuroendocrine tumors (NETs) [1,2]. Radiolabeled somatostatin agonists have shown great clinical value in diagnosis and management of patients with NETs [3,4]. However, recent literature reports have shown that radiolabeled somatostatin antagonists may perform better than radiolabeled somatostatin agonists in terms pharmacokinetics and tumor visualization [5,6]. Amongst the several somatostatin antagonists investigated, ^{68}Ga-NODAGA-JR11 has demonstrated encouraging results. Consequently, ^{68}Ga-NODAGA-JR11 has now reached phase-II clinical trials for detection of NETs [1,5]. ^{68}Ga-NODAGA-JR11 is reported to exhibit higher sensitivity and better image contrast than ^{68}Ga-labeled sstr agonists (^{68}Ga-DOTA-TATE/TOC/NOC) in detection of NETs [5,6]. The higher sensitivity is attributed to lower uptake of ^{68}Ga-NODAGA-JR11 in liver, intestine and pancreas in contrast to ^{68}Ga-labeled sstr agonists.

The simple kit-type radiolabeling would encourage hospitals to participate and facilitate the evaluation of ^{68}Ga-NODAGA-JR11 in broader patient population. Freeze-dried kits containing pre-assembled sterile ingredients in dry powder form allow for simple and hassle-free preparation of the radiopharmaceutical at hospital radiopharmacy [7]. The single-vial kit is particularly attractive for formulation of ^{68}Ga-radiopharmaceuticals as the short half-life of Ga-68 ($t_{½}$ = 68 min) necessitates for rapid and robust radiolabeling protocol.

Present study reports optimization of different parameters for successful development of a single-vial NODAGA-JR11 freeze-dried kit. The kits were formulated with $^{68}GaCl_3$ eluted from ITG ^{68}Ge/^{68}Ga generator (Isotope Technologies, GmbH, Germany) and evaluated in patients with NET.

Materials and Methods

Optimization of radiolabeling parameters for NODAGA-JR11 (piCHEM, Austria) was carried out by addition of $^{68}GaCl_3$ (0.05 N HCl) from ^{68}Ge/^{68}Ga generator (ITG, Germany). Radiolabeling was performed varying different parameters such as amount of peptide, amount of buffer, incubation time and temperature to optimize conditions prior to kit formulation. Freeze-dried NODAGA-JR11 kits were prepared based on the optimized wet chemistry protocol. A 10 vial batch of JR11 kits was prepared with each kit vial containing 50 µg NODAGA-JR11 and 11.5 mg sodium acetate.

For the kit-based preparation of ^{68}Ga-NODAGA-JR11,$^{68}GaCl_3$ (2 mL, 3-15 mCi) eluted in 0.05 N HCl was added and the reconstituted kit vial was incubated at 90^{0}C for 10 min. Radiochemical yield of ^{68}Ga-NODAGA-JR11 was determined by performing paper chromatography (PC) and reversed phase high performance liquid chromatography (RP-HPLC).

In vitro stability of the kit-formulated ^{68}Ga-NODAGA-JR11 was evaluated at 1 h and 2 h post preparation. Long term shelf-life of kits was assessed by reconstitution at periodic intervals (1 month and 3 months) and subsequent analysis of the radiolabeling yield. The pharmacokinetics of kit formulated ^{68}Ga-NODAGA-JR11 was studied by performing biodistribution studies in normal Swiss mice. Preliminary clinical evaluation of kit-formulated ^{68}Ga-NODAGA-JR11 was carried out in AIIMS, Bhubaneswar after obtaining approval from institutional ethical committee clearance.

Results and Discussion

^{68}Ga-NODAGA-JR11 could be formulated using freeze-dried kits in >95% radiochemical yield (Fig. 1). Kit-formulated ^{68}Ga-NODAGA-JR11 stored at room temperature was observed to be stable till 2 h post-reconstitution as there was no significant change in the HPLC profile. Freeze-dried kits have

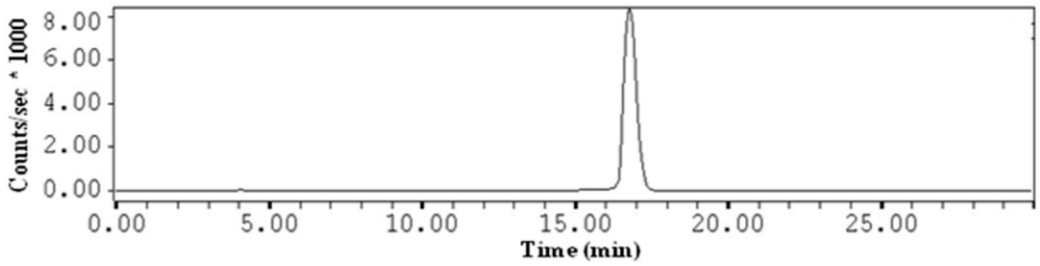

Fig.1: Radio-HPLC chromatogram of ^{68}Ga-NODAGA-JR11 formulated using freeze-dried kit.

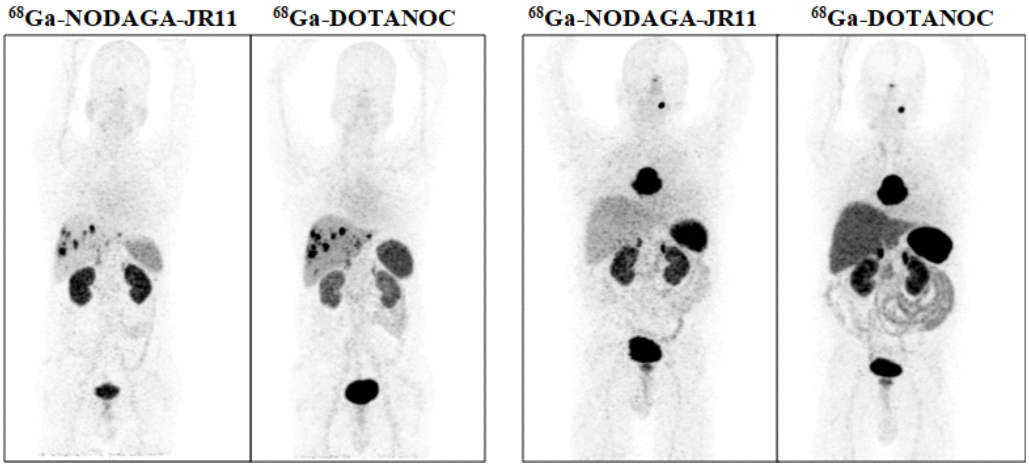

Fig.2: PET/CT scan of ^{68}Ga-NODAGA-JR11 and ^{68}Ga-DOTANOC in NET patients.

been tested to be stable till 3 months post-preparation when stored at 0°C.

Preliminary clinical evaluation in NET patients indicated high uptake in primary as well as metastatic lesions. Comparative PET/CT images with ^{68}Ga-DOTA-NOC (in the same patient) suggested comparable tumor uptake but better liver and background clearance for ^{68}Ga-NODAGA-JR11. Present studies indicate promising potential of ^{68}Ga-NODAGA-JR11 towards detection of liver metastatic lesions (Fig. 2).

Conclusion

Single-vial NODAGA-JR11 freeze-dried kits amenable for formulation with $^{68}GaCl_3$ eluted in 0.05 N HCl from ITG ^{68}Ge/^{68}Ga generator was developed. These kits resulted in simple and quick preparation of ^{68}Ga-NODAGA-JR11 in high yields. Kit-formulated ^{68}Ga-NODAGA-JR11 could clearly identify the primary as well as metastatic lesions with good accuracy and specificity in patients with NETs. The facile formulation of ^{68}Ga-NODAGA-JR11 using the freeze-dried kit provides a valuable advantage, facilitating its use in clinical settings.

Acknowledgement

Authors are thankful to Dr. P. K. Mohapatra, Associate Director, Radiochemistry & Isotope Group and Dr. Tapas Das, Head, Radiopharmaceuticals Division for their support and encouragement. Authors acknowledge the help rendered by the staff of the animal house facility of Bhabha Atomic Research Centre. The authors are also thankful to Dr. Kanhaiya Agrawal of AIIMs, Bhubaneswar for performing the clinical evaluation studies.

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