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An automated synthesis of ^{177}Lu-EDTMP as an efficient bone-seeking therapeutic radiopharmaceutical

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Abstract. – OBJECTIVE: Radiolabeled bisphosphonates have found wide clinical use in nuclear medicine for palliative therapy of bone metastases. ^{177}Lu-EDTMP was used to relieve metastatic bone pain in patients with breast or prostate cancer. The therapeutic efficacy of ^{177}Lu-EDTMP at 1-, 3-, 6-, and 8-weeks post-therapy was evaluated using Standard Pain Scoring Assessment Criteria. In addition, toxicity was evaluated in terms of hematological parameters using the Common Terminology Criteria for Adverse Events V4.0.

PATIENTS AND METHODS: A fully automated synthesis of ^{177}Lu-EDTMP was achieved in this study with high radiochemical efficiency and high radiochemical purity. During the study, 75 patients (57 M: 18 F, mean age: 68.0 ± 11.1 years) of breast/prostate cancer with documented skeletal metastases were included. Patients were administered intravenously with ^{177}Lu-EDTMP at a dose rate of 22.2-37.0 MBq/kg following a fully automated synthesis of ^{177}Lu-EDTMP using a disposable cassette system.

RESULTS: Among the 75 patients all treated with ^{177}Lu-EDTMP, 59 patients were responsive and the remaining 16 patients did not respond to the therapy. Mean pain score values in the responder group were 5.60 ± 0.5, 4.3 ± 0.1, 2.6 ± 0.4 and 1.4 ± 0.7 at weeks 1, 3, 6, and 8, respectively. Also, the mean pain score decreased from a baseline score of 7.6 ± 1.6 to 1.4 ± 0.7 at week 8 in the responder group. Statistical analysis of the pain score data showed a significant decrease in pain score after each radiopharmaceutical treatment, compared to the baseline scores (p <0.0001). Mild to severe toxicity was observed in two patients each treated with ^{177}Lu-EDTMP.

CONCLUSIONS: These findings demonstrated that the ^{177}Lu-EDTMP radiopharmaceutical could be used safely to achieve considerable therapeutic efficacy, in metastatic bone pain palliation together with the safe clinical application and low radiation exposure during preparation.

Key Words:
Automated system, Radiopharmaceuticals, ^{177}Lu-EDTMP, Osseous bone metastates, Pain palliation.

Introduction

Breast and prostate cancers are among most common types of the human cancers[1,2]. Moreover, bone metastases could be seen in these cancers frequently, as well as in other cancer types, such as lung and liver cancers. Unfortunately, fatal consequences could occur in these cases unless earlier and convenient therapy is applied[3]. Bone metastases can cause bone pain, spinal cord compression, bone fractures, and reduces quality of life, dramatically[4]. Chemotherapy, immunotherapy, endotherapy and bisphosphonates constitute various treatment approaches for bone metastases[5-9]. However, more recently, radiopharmaceuticals have been playing important role for the therapeutic approaches to bone metastases and are classified into two distinct groups: calcimimetic and phosphonate-coupled radiopharmaceuticals. Common calcimimetic radiopharmaceuticals consist of Radium-223[10], strontium-89[11] and phosphorus-32[12] and, due to this pharmacokinetic trait, these agents could be absorbed selectively by metastatic bone sites. Therefore, they can be utilized without any ligand and/or linker. On the other hand, bisphosphonates can be used as favorable radionuclide vehicles for the therapeutic treatment because of their affinity to hydroxyapatite crystals of bones[13]. EDTMP [ethylenediamine tetra (methylene phosphonic acid)], is a phosphonate-coupled chelator that is featured for the pain palliation caused by metastatic bone cancer[14]. This

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chelation takes place via deprotonation of EDTMP ligand, provided highly stable complex with trivalent lanthanide nuclides (Ln^{III}-EDTMP) (Figure 1).

^{177}Lu-EDTMP is a therapeutic radiopharmaceutical has been frequently utilized for the bone pain palliation due to its favorable physical properties (T½ = 6.73 days, Eβmax = 497 keV; Eγ = 113, 208 keV)[15,16]. In addition to destroying of cancer cells that are in range of β-emission, ^{177}Lu-EDTMP provides scintigraphic image of the bone metastases through its γ-emission.

To the best of our knowledge, ^{177}Lu-EDTMP assisted radiopharmaceutical therapy was applied to the patients in Turkey for the first time in our center. The therapeutic efficacy of ^{177}Lu-EDTMP was evaluated for pain palliation in prostate and breast cancer patients with multiple bone metastases. Pain response was measured by following appropriate clinical criteria for pain assessment to evaluate therapeutic effect of the ^{177}Lu-EDTMP radionuclide therapy. Automated synthesis method was successfully afforded by our team to obtain high radiochemical purity with desirable high yields. Quality control was also well established by isocratic method at radio-HPLC and radio-TLC. This study aimed to describe a fully automated synthesis of ^{177}Lu-EDTMP for the palliation of metastatic bone pain for the first time and evaluate of the therapeutic efficacy with low radiation exposure during preparation.

Patients and Methods

Chemistry

$^{177}LuCl_3$ was obtained from Polatom (Otwock, Poland) with a specific activity of around 750 GBq/mg, EDTMP cold kit was purchased from Pars Isotope (Tehran, Iran) and Whatman No. 3 paper was also purchased from Whatman Company.

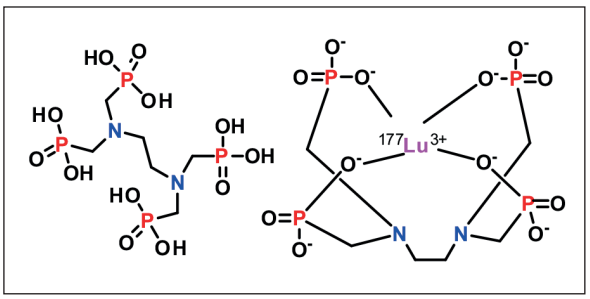

Figure 1. Structures of EDTMP [ethylenediamine tetra (methylene phosphonic acid)] and ^{177}Lu-EDTMP complex.

Characterization Methods

The HPLC and TLC analyses were performed by Miniscan Radio-TLC Scanner and Modular-Lab HPLC which Eckert & Ziegler (Berlin, Germany) devices.

Radiolabeling Procedure

EDTMP kit solution (50.0 mg/1.0 mL) was labeled with $^{177}LuCl_3$ solution (0.2 mL, 100 mCi) at 80°C over 30 minutes at pH 7. The product is diluted with 4.0 mL saline and subsequently purified *via* a weak cation exchange cartridge (CM cartridge) to remove metal impurities. Finally, the solution was passed through a millipore filter (0.22 μm) and was injected intravenously after more than 99% radiochemical purity.

Patients

75 patients (57 M: 18 F, mean age: 68.0 ± 11.1 years) with breast or prostate cancer and multiple bone metastases and were enrolled during the study period (June 2019-July 2020) with the approval of the Local Ethics Committee, in accordance with the "Helsinki Declaration on Patient Safety".

Before the ^{177}Lu-EDTMP administration, each patient underwent a detailed history, clinical examination, bone scintigraphy with ^{99m}Tc-methylene diphosphonate (^{99m}Tc-MDP) and various blood examinations. Patients with severe bone pain despite taking analgesics only, and positive multiple skeletal metastases in ^{99m}Tc-MDP bone scintigraphy performed in the last 8 weeks, who were not candidates for local external beam therapy, and who gave written and informed consent were included in the study. Furthermore, patients who had not received any chemotherapy or external irradiation during the last 4-12 weeks and had normal hematological/renal parameters were also included in the study. Patients with a history of pre-existing cytopenia, super-scan appearance on bone scintigraphy, impaired renal function, reaction to radionuclide/radiopharmaceutical administration, and patients with pregnancy/lactation that is absolute contraindication, were excluded from the study. In all patients, whole body (anterior and posterior) bone scintigraphy was performed at the 2nd hour following intravenous administration of approximately 555.5-740.0 MBq ^{99m}Tc-MDP using a double-headed gamma camera.

The radiolabeled product was subjected to routine quality checks before each use. ^{177}Lu-EDTMP was administered intravenously at a dose rate of 22.2-37.0 MBq/kg. The safety of ^{177}Lu-EDTMP radionuclide therapy was evaluated *via* Common Terminology Criteria for Adverse Events[17].

Imaging was done using an NM/CT 860 computed tomography coupled single photon emission tomography (SPECT/CT) (General Electric, Milwaukee, WI, USA) fitted with a low energy, high resolution collimator. Whole body (anterior and posterior) images were acquired in a 1,024 × 256 matrix at a scanning speed of 10.0 cm/min while patients on supine position. Each imaging of patients was performed 6 hours after the radioactivity administration. The first anterior and posterior image dataset acquired at sixth hour demonstrated 100% of the administrated activity of ^{177}Lu-EDTMP. The efficacy of the radionuclide at 1, 3, 6 and 8 weeks after therapeutic treatment was evaluated using Standard Pain Scoring Assessment Criteria[18]. Based on this assessment, the response was labeled (a) complete response when the pain score was below 3.0, (b) partial response when the pain score ranged from 4 to 8, and (c) no response when the pain score was over 8 and does not change compared to the baseline score. Pain scores between responders and non-responders in the two groups were compared using the paired Student's *t*-test. For all tests, $p < 0.05$ was considered significant at 95% confidence interval. Data were analyzed using the SPSS 21.0 (Armonk, NY, USA).

Results

The average administered doses of ^{177}Lu-EDTMP were 1934.1 ± 326.8 (range 925-2.857) MBq and did not differ significantly between patients, since we used 22.2-37.0 MBq/kg of the radiopharmaceutical. Imaging data demonstrated that ^{177}Lu -EDTMP showed rapid blood and soft tissue clearance. Skeletal metastatic lesions displayed increased uptake of radiopharmaceuticals, which were consistent with ^{99m}Tc-MDP bone scanning (Figure 2).

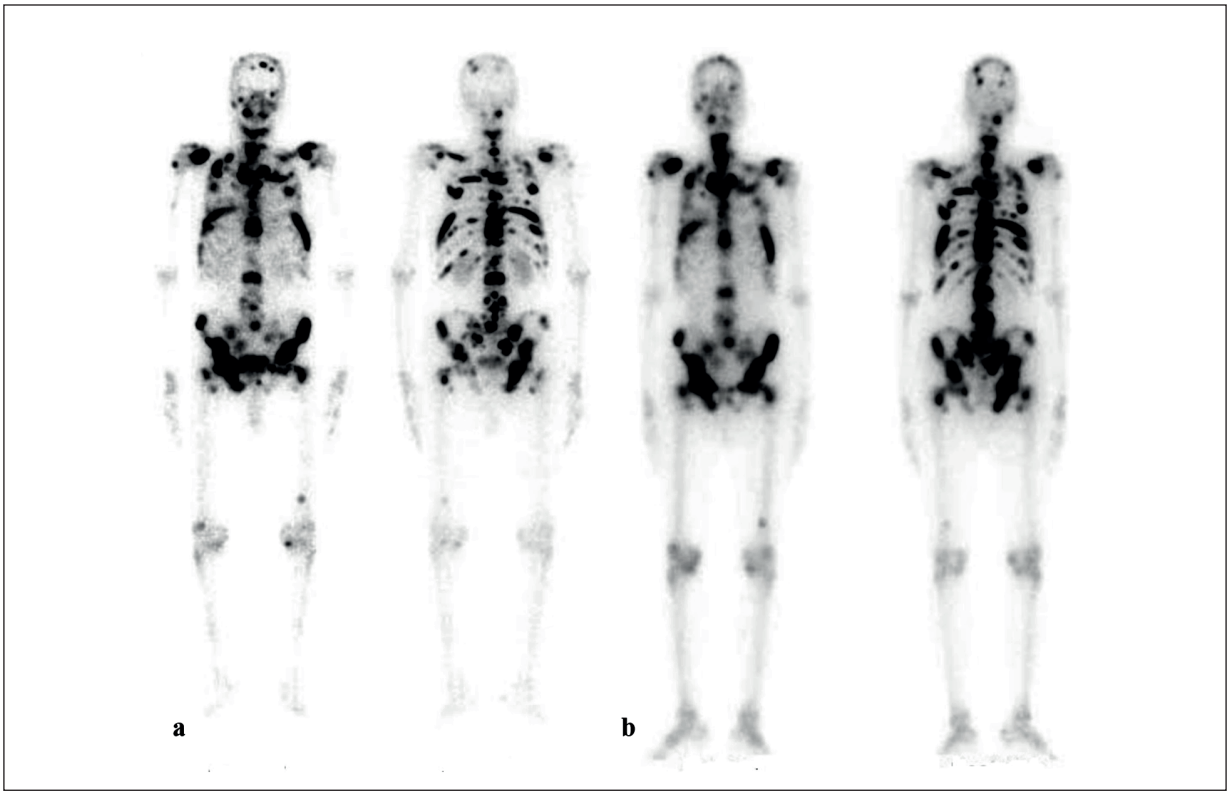

Figure 2. Metastatic lesions were evaluated on the pre-treatment (a) ^{99m}Tc-MDP and post-treatment (b) ^{177}Lu-EDTMP bone scanning. The most common metastatic lesions were observed in calvarium, sternum, vertebrae, proximal upper extremities, pelvic bones, femur, and costal bones.

Table I. Baseline and post-treatment mean pain scores: Mean pain scores decreased after the ^{177}Lu-EDTMP therapy in a statistically significant manner compared to the baseline scores.

Time (weeks)	Mean Pain Score ± SD
0	7.6 ± 1.6
1	5.60 ± 0.5*
3	4.3 ± 0.1*
6	2.6 ± 0.4*
8	1.4 ± 0.7 *

*Indicates *p*-value of < 0.0001 at 95% confidence interval.

Among the 75 patients who all treated with ^{177}Lu-EDTMP, 59 patients were responsive and the remaining 16 patients did not respond to the therapy. Mean pain score values in the responder group were 5.60 ± 0.5, 4.3 ± 0.1, 2.6 ± 0.4 and 1.4 ± 0.7 at weeks 1, 3, 6, and 8, respectively (Table I).

Also, the mean pain score decreased from a baseline score of 7.6 ± 1.6 to 1.4 ± 0.7 at week 8 in the responder group. Statistically significant decrease in pain scores were observed after each radiopharmaceutical treatments, compared to the baseline scores, during evaluation period (p <0.0001*)*. No significant changes in hematological parameters were noted compared to baseline during the follow-up periods of the treatment with any of the administered doses (Table II). However, mild to severe hematological toxicity was observed in two patients each treated with ^{177}Lu-EDTMP. These findings demonstrated that the ^{177}Lu-EDTMP radiopharmaceutical could be used safely to achieve considerable therapeutic efficacy, in metastatic bone pain palliation. Regarding of survival, 66 of 75 patients survived until the end of 8 weeks of the study. Further back, among the other 9 patients: 6 patients died at week 8, 2 at week 4, and 1 patient within 3 weeks of treatment.

Discussion

Radiolabeling of EDTMP with ^{177}Lu was performed using an ML-EAZY system (Figure 3) which consists of automatically enhanced pressurized systems attached to body of synthesizer and disposable cassette set up on the top of it. EDTMP cold kit dissolved by 1.0 ml saline solution was added to vial containing ^{177}Lu that is connected to the disposable cassette. The reaction was started by introducing heat to the system (80°C) and completed within 30 min. Whole process was implemented in the synthesis template without any manual interference. The consequent product was diluted with sufficient amount of saline in order to transferred through the pre-conditioned light CM cartridge and millipore filter (0.22 μm), attached to the product vial. Following the completion of the reaction, cassette was automatically ejected. Thereafter, radioactivity of product and the system components were measured to determine the radiochemical yield of the product. Subsequent to successfully automated synthesis of the ^{177}Lu-EDTMP, clinical utilization of the therapeutic agent was investigated.

Irradiation of metastatic bone lesions through the short-ranged beta emitters provides significantly favorable pain palliation in patients have multiple skeletal metastases with minimal radiotoxicity on surrounding normal tissue. In this study, 75 patients were subjected to the intravenous ^{177}Lu-EDTMP at a dose rate of 22.2- 37.0 MBq/kg. Accurate mapping was required before and after the dose administration in these patients in order to ensure significant activity delivery to the regions of interest. Therefore, it was important that corresponding lesions in ^{99m}Tc-MDP and ^{177}Lu-EDTMP bone scans were coherent[19].

Regarding the recent studies, Shinto et al[20] used ^{177}Lu-EDTMP produced in-house similarly, at a fixed dose of 3,700.0 MBq and reported complete pain response after 12 weeks. Yuan et al[21]

Table I. Baseline laboratory parameters of patients treated with the ^{177}Lu-EDTMP (Mean ± SD): There was no significant adverse effect throughout the 8 weeks of follow-up compared to the baseline levels in terms of hematological parameters.

Laboratory studies	Laboratory values at different time intervals				
	Pre-therapy	1. Week	3. Week	6. Week	8. Week
Hemoglobin (g/dL)	11.14 ± 0.48	10.7 ± 0.30	9.4 ± 0.81	8.8 ± 1.21	8.9 ± 1.95
Absolute WBC counts (/mm^3 of blood)	8.790 ± 1,35	7.410 ± 1.24	6.85 ± 1.39	6.3 ± 1.68	6.6 ± 1.54
Neutrophil counts (/mm^3 of blood)	5.500 ± 1.121	3.875 ± 740	2.696 ± 4.53	2.198 ± 3.61	2.357 ± 5.47
Platelet counts (/mm^3 of blood)	2.71 ± 0.43	2.14 ± 0.41	1.71 ± 0.33	1.31 ± 0.27	1.34 ± 0.47

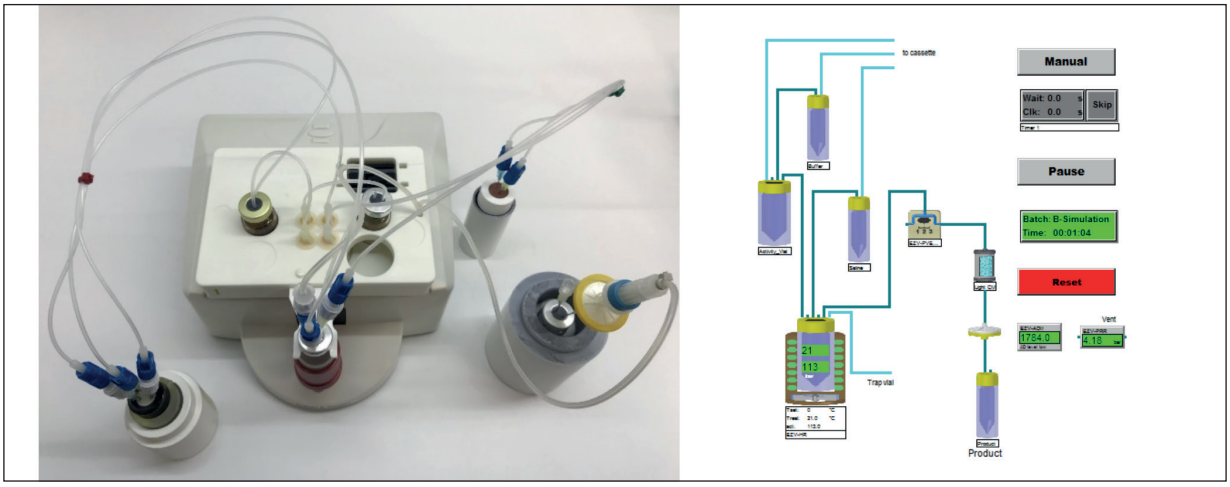

Figure 3. **(a)** Fully automated disposable cassette system (Modular-Lab ML-EAZY) **(b)** Software system.

also reported that the fixed dose of ^{177}Lu-EDTMP of 2,590 MBq showed an 80% response rate, remarkably. In a similar manner, Agarwal et al[22] reported an overall response rate of 86% in a group of 44 patients treated with ^{177}Lu-EDTMP. Furthermore, complete, partial, and minimal response rates were observed in 13, 48 and 25% of patients enrolled, respectively. These results are comparable to the ^{89}SrCl2 radiopharmaceutical widely used for bone pain palliation, especially in western countries. ^{177}Lu-EDTMP has some advantages over ^{89}SrCl2 in terms of cost effectiveness and toxicity characteristics[23]. There are various publications based on toxicity related to the aforementioned therapeutic radionuclides[24,25]. However, clinical studies have shown that 177Lu-EDTMP radiopharmaceutical is considerably safe due to the absence of acute pain exacerbation and lack of dramatic changes in hematological parameters. Shinto et al[20] also did not report any incidence of toxicity in their preliminary study using 3.700.0 MBq dose of ^{177}Lu-EDTMP.

This study was limited by the absence of a control group, and lack of long-term follow-up. Survival rates could not be assessed because of short observation period. Therefore, further studies of longer duration are needed to assess survival rates, safety, and efficacy of ^{177}Lu-EDTMP.

Conclusions

A fully automated synthesis of ^{177}Lu-EDTMP for the pain palliation of multimetastatic bone lesions was described for the first time. EDTMP was successfully radiolabeled with ^{177}Lu at high radiochemical yields with absolute radiochemical purity using GMP-compliant single-use, sterile, disposable cassettes. Reaction was completed within 30 min at 80ºC without any manual interference. This study demonstrated that significant pain response could be achieved in palliative therapy of bone metastases together with the safe clinical application and low radiation exposure during preparation.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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