

Scientific Session-4 Neuroendocrine Tumours – 2

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Concomitant chemotherapy, radioimmunotherapy of lymphoma

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Radiosensitizing chemotherapy has been shown to enhance response rates to conventional external beam radiotherapy of solid tumours. Extrapolation of combination chemotherapy is currently being evaluated in conjunction with radionuclide therapy, in respect of lymphoma and neuroendocrine malignancy. A phase IIA clinical trial of ¹⁷⁷Lu-octreotate radiolabeled peptide therapy combined with radiosensitizing capecitabine chemotherapy was performed in 29 patients with progressive disseminated unresectable neuroendocrine tumours. Follow-up after 6 months after 4 cycles of 7.8 GBq ¹⁷⁷Lu-octreotate/1650 mg/m² capecitabine daily for 2 weeks yielded an objective response rate (ORR) 75% and median time to progression (TTP) 14 months. There was no additive toxicity in comparison with ¹⁷⁷Lu-octreotate radiolabeled peptide therapy alone. A phase I dose-escalation clinical trial of the addition of temozolomide to the ¹⁷⁷Lu-octreotate/ capecitabine combination is in progress and preliminary results will be presented and compared with reported outcomes of chemotherapy regimens of capecitabine/ temozolomide chemotherapy without radiolabeled peptide. The use of conditioning ¹³¹I-rituximab combined with BEAM chemotherapy prior to autologous stem cell transplantation for aggressive non-Hodgkin lymphoma is established practice in our institution and avoids the toxicity of total body irradiation. We have supplemented this experience with the use of ¹³¹I-rituximab radioimmunotherapy consolidation after an abbreviated 3 cycle course of standard R-CHOP 21 chemotherapy, in first-line Stage III follicular non-Hodgkin lymphoma. A pilot study has been commenced with the objective of mitigating the toxicity of the standard 6 cycle R-CHOP regimens. This combination radionuclide chemotherapy approach will be compared with our current phase II trial results of first-line ¹³¹I-rituximab radioimmunotherapy of follicular non-Hodgkin lymphoma.

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Bisphosphonates conjugated to macrocyclic ligands: Ga-68 based PET/CT imaging tracers vs. Lu-177 based therapy.

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No abstract available

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Treatment of neuroendocrine tumors with radiolabeled peptide: The Chilean Experience

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Introduction: Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasm that affects organs from the neuroendocrine system and from the gastrointestinal and bronchial tract. The most frequent localizations are intestine (carcinoid), pancreas and bronchi. Its incidence in the United States has increased from 1,5 by 100,000 inhabitants in 1983 to 6,7 by 100,000 inhabitants in 2008. Even though NETs have been considered relatively “benign” recent data indicate a more ominous prognosis than it was thought with a 5 years survival rate of only 57% for well-differentiated tumors.

The only truly curative option for NETs is surgery if they are detected as localized disease. However, in a high percentage of patients the diagnosis is done in advanced stages when treatments only have the intention to improve survival and the quality of life. Therapeutic alternatives in disseminated disease include: symptomatic medical treatment with somatostatin (SS) analogs, chemotherapy, embolization, chemo-embolization, immunotherapy, radio-frequency ablation, radiotherapy and molecular therapy with SS analog receptors (SSR) labeled with radionuclides. This last option has been considered as one of the most promising tools in the treatment in advanced stages.

NETs are characterized by over-expression of SSR in their cellular surface. There are 5 known subtypes of SSR (ss₁₋₅) defined by 5 different genes. This explains its different representation in diverse types of tumors. In the present study we analyzed our pioneer experience in Latin America using SS analogues labeled either with ⁹⁰Y or ¹⁷⁷Lu to treat patients with advanced NETs.

Materials and Methods: Patients: After informed consent, we evaluated 40 patients, 22 women and 18 men, average age 50,3 years (range 12-74), with histologically proven diagnosis of NET treated with radionuclide labeled SS analogs. All of them had demonstration of multifocal over-expression of SSR by means of SPECT with ¹¹¹In-DOTATOC or PET/CT with ⁶⁸Ga-DOTATATE images. Hematological, biochemical and renal function were evaluated in all of them. The primary tumor was located in pancreas in 17, intestine in 14, rectum in 1, thymus in 1, ovary in 1, bronchial in 1 and unknown in 5. Secondary locations were in liver, mesentery, mediastinum,

retroperitoneum and orbit. **Therapeutic Procedure:** All patients were hospitalized for 24 hours. Before the therapeutic procedure, patients had a 6 hour fasting period and received intravenous antiemetic medication, over-hydration and renal protection with intravenous aminoacid overload. Since June 2006, we added intravenous succinylated gelatin as an additional renal protection. The patients were discharged on the following day after the acquisition of nuclear medicine images. In the present study, a total of 139 doses were administered, 63 of them with DOTA-[Tyr³, Thr⁸]-Octreotide (DOTATOC) labeled with ⁹⁰Y, 29 with DOTA-[Tyr³]-Octreotate (DOTATATE) and 47 with ¹⁷⁷Lu-DOTATATE (Nuclear CGM, Chile) in doses that fluctuated between 925 and 8,880 MBq (25 - 240 mCi) with an average dose of 3533.5 MBq (95.5 mCi). The maximum accumulated dose was of 28.67 GBq (775 mCi).

Radiochemistry: The conjugates DOTATOC or DOTATATE (ABX GmbH, Germany) were labeled either with ⁹⁰Y or ¹⁷⁷Lu (MDS Nordion, Canada or Perkin Elmer, USA). Radionuclides were obtained in neutralized chlorate solution with gentisic buffer /Sodium acetate at pH 5.0. The peptide was added in a saline solution of 2 µg/µL, adjusting the relation of µg conjugate/ mCi of the radionuclide to 1.5. The reaction mixture was warmed up during 30 minutes to 90°C. Radiochemical purity was determined by liquid chromatography with fine layer using TLC-SG 60-Merck as the support and 0,1 M of Na-citrate as the solvent and/or Sep-Pak mini-columns activated with acetate buffer pH 5,0 and eluted with Methanol or ethanol. **Control imaging:** After the administration of each therapeutic dose, whole body planar images and specific spot views were obtained in a gamma-camera using the Bremsstrahlung radiation of ⁹⁰Y or the gamma-ray emissions of ¹⁷⁷Lu.

Results: Clinical response: The patients were evaluated according to the symptomatic clinical answer, laboratory tests, serial follow-up images with ¹¹¹In-DOTATATE or bone scintigraphy. Post-therapy images with ⁹⁰Y or ¹⁷⁷Lu were evaluated by tumor/background ratio, comparing the SUV when ⁶⁸Ga-DOTATATE PET/CT was available or lesion size in computed axial tomography according to the characteristics on each particular case. According to these parameters the response was classified as progression of disease, stabilization, partial or complete response.

Hematological toxicity: Only grade 1 and 2 toxicity in the red series, neutrophils or platelets was observed. Hemoglobin level fell in 6,4% of the initial value at the 45th day post-treatment. Grade 3 thrombocytopenia was observed in 3 patients and grade 4 in 1 patient, all of them presented fast recovery not requiring stimulating agents or blood transfusions.

Renal toxicity: There were no significant changes in the creatinine clearance during the follow up period of up to 7 cycles of radiopeptide therapy. In one 70 years old patient with liver metastases in 2004, her creatinine increased up to 1.78 mg/dl after receiving 5 cycles with ⁹⁰Y DOTATOC.

Radiochemical purity: The radiochemical purity of ⁹⁰Y-DOTATOC, ⁹⁰Y-DOTATATE and ¹⁷⁷Lu-DOTATATE determined by liquid chromatography always over 99%.

Discussion: The therapeutic alternatives in advanced NETs are limited and most options are addressed to improve the survival rate and the quality of life. One of the greatest advances in nuclear medicine in the last 15 years has been

the inclusion of diverse peptides labeled with radionuclides for diagnostic and therapeutic purposes. These radiopharmaceuticals are a clear example of the unique capacity of nuclear medicine to recognize molecular and functional processes to provide a high radiation dose to specific targets by systemic route.

Because of the permanent evolution of this therapeutic modality, we have had to adapt to new protocols according to the advance of the international experience. When we initiated our experience in January of 2004 we used ⁹⁰Y-DOTATOC and latter DOTATATE due to its greater affinity to the SS₂ receptors. In order to reduce the renal retention of the radionuclide we have incorporated throughout the study the double protection of the kidneys, using intravenous aminoacid overload and succinylated gelatin. Additionally, we prefer to use ¹⁷⁷Lu over ⁹⁰Y as the radionuclide of choice due to published data indicating a lower kidney radiotoxicity. In our series we do not have significant renal function deterioration.

Our results show that the procedure is safe with little hematological toxicity. In this series we observed grade 1 or 2 anemia, neutropenia or thrombocytopenia, all reversible. The more sensible blood elements were lymphocytes with grade 3 lymphopenia in 4 patients and grade 4 in one patient, all of them also with spontaneous recovery.

Our data suggest a clinical response similar to what has been published before, showing good outcome in 74% of the patients. This represents a partial reduction of the tumor mass in 61%, stabilization of the disease in 8% and complete remission in 5% of the cases. In all the patients a good symptomatic response was achieved, including weight recovery, pain release and better quality of life. Due to the limited number of patients in this series and short follow-up period it has not been possible yet to evaluate survival rate; nevertheless, there are published data that indicate that with similar protocols it is possible to prolong the survival rate between 23 to 69 months when comparing radiopeptide therapy results with other therapeutic options.

Conclusions: The use of ⁹⁰Y/¹⁷⁷Lu-DOTATATE allows treating a large number of patients suffering advanced SSR positive tumors without significant side effects. In this series we have observed objective tumor reduction and improvement in the quality of life in most of the patients. Our experience, like from other authors, indicates that treatment of patients with advanced NETs with radiolabeled SS analog peptides is a safe and effective method yielding clear clinical benefits to most of them. Furthermore, this therapeutic modality represents a new frontier for Nuclear Medicine specialist as an important part of the multidisciplinary oncology team.

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Survival benefits and efficacy of Peptide Receptor Radionuclide Therapy (PRRT) using Y-90/Lu-177 DOTA-TATE in Pancreatic Neuroendocrine Tumors (pNET)

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Aim: High expression of somatostatin receptors on pNET enables peptide receptor radionuclide therapy (PRRT)

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using Y-90/Lu-177 DOTA-TATE. The aim of this study was to evaluate the overall survival and to assess the response to PRRT. Method: We analyzed 107 patients (mean age 60 yrs) with progressive pNET treated with 1-7 cycles of PRRT using Y-90/Lu-177 DOTA-TATE. Response assessment was done in 54 patients receiving more than 3 cycles of PRRT and followed up for a minimum duration of 3 months. Results: Mean/Median duration of follow-up after first diagnosis was 107/ 58.5 months. 29 patients (27%) died at an average age of 58 yrs. 26 (24 %) had nonfunctional, whereas 84(76%) had a functional pNET. Tumor localization: head - 31, body- 16, tail and cauda -41, total pancreas -4, body and tail -9, head and body - 6. Overall, 11 patients had gastrinoma, 7 glucagonoma and 2 insulinoma. Metastases in the liver were present in 99 patients (92.5%), in lymph nodes in 58 (54%) and in bone in 38 patients (36.4%). 44 patients were pretreated with chemotherapy (41%), 52 by surgery (48.6%) and 46 with sandostatin (43%). Objective response (complete remission, partial remission and minor response) was seen in 52 % of the patients whereas in 39% of the patients the previously progressive disease was stabilized; 9% had progressive disease. Median duration of survival from the time of first diagnosis was 189 months. Median survival in patients with pNET in the pancreatic head was much shorter (132 months) as compared to tumors located in the pancreatic body/cauda/tail (256 months). Mean survival (median not achieved) in nonfunctional pNET was 148 months as compared to mean survival of 341 months for functional pNET (median survival of 135.6 months). Mean survival (median not achieved) in patients with Ki 67 < 20% was found to be 183 months vs. 73 months for those who had Ki 67 > 20%. Conclusion: PRRT is an effective therapy option for pNET. Patients with pNET in the head of the pancreas and high-grade tumor (Ki67 > 20%) have a poorer prognosis.

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Comparison between clinical results of PRRT with 90Y-DOTA TATE and 90Y/177Lu- DOTATATE

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Peptide Receptor Radionuclide Therapy (PRRT) using radiolabelled somatostatin analogues is a promising treatment option for patients with disseminated and inoperable neuroendocrine tumours. The idea of the combined treatment with high-energy 90Y (for larger lesions) and the low-energy 177Lu (for smaller lesions) was considered. The aim of our study was to compare results of PRRT with 90Y-DOTATATE and mixed 90Y/177Lu-DOTATATE. Materials and methods: 36 patients with diffuse neuroendocrine tumors were enrolled in the study and divided into two groups: GroupA (18 pts: 8 men, 10 women, aged 56±12) was treated with 90Y DOTATATE only; GroupB (18 pts: 7 men, 11 women, aged 56±11) was treated with 90Y/177Lu DOTATATE. Blood tests for hematology, kidney and liver function, and CgA were evaluated before therapy. All patients underwent CT scans

and SRS with 99mTc-HYNIC-TATE. Response of treatment in CT was evaluated according to WHO standard criteria. Treatments were repeated, up to a total calculated dose – 200 mCi/m², 100 mCi was usually administered per one course; in mixed doses 90Y to 177Lu DOTATATE was 1:1. Median interval between the treatment courses in GroupA was 36 days, in GroupB - 49 days. Mixed amino-acids infusion over 8 hours was used for kidney protection. Results: In GroupA median time of survival was 33.7 months, in GroupB median survival was not reached. Comparison of overall survival probabilities showed significantly higher survival in group treated with 90Y/177Lu Lu DOTATATE, p=0.04. The calculated probability of 24 months survival was 61% in GroupA and 87% in GroupB. Median time to progression in GroupA was 18.9 months and in GroupB 29.4 months; difference was not statistically significant, p>0.1. Probability of 12 months progression free survival was 67% in GroupA and 77% in GroupB. 12 months follow-up: (Group A vs Group B): stable disease - 9 vs. 11 pts, regression - 2 vs. 2 pts, progression 3 vs. 3 pts. Respectively 4 and 2 pts died. 24 months follow-up: (Group A vs. Group B): stable disease - 5 vs. 6 pts, progression - 4 vs. 3 pts. Side effects in both groups were rare and mild Conclusions: 1. Significantly longer time of survival was observed in-group treated with 90Y/177Lu DOTATATE than in those treated with 90Y-DOTATATE only 2. It seems that overall survival time and time to progression rather than WHO criteria should be used to evaluate response to therapy. This study was supported by Polish Ministry of Health Research Grant (4-PW/102/4283/85195)

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Ensayos preclínicos del ¹⁷⁷Lu-DOTA-Minigastrina para su potencial uso en PRRT

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Introducción: La minigastrina (MG) es un péptido de 13 aminoácidos que ha sido modificado para disminuir su captación renal (His-His-GLu-Ala.Tyr-Gly-Trp-Met-Asp-Phe-NH₂) y que pertenece a la familia de péptidos que se unen al receptor CCK-2, el cual es un posible blanco en la terapia radionucleídica de receptores peptídicos (PRRT) para el tratamiento de varias especies tumorales.

Objetivo: Obtener ¹⁷⁷Lu-DOTA-Minigastrina (empleando ¹⁷⁷LuCl₃ de Ae= 6.36-9.73 Ci/mg de ¹⁷⁶Lu, de producción local) con una alta pureza radioquímica (PR), la mayor actividad específica (Ae) posible, realizar los controles de estabilidad in-vitro e in-vivo, el cálculo de dosis en ratones normales y su extrapolación a un modelo humano.

Materiales y Métodos: Para la marcación se mezclaron 20 µg de DOTA-MG en buffer acetato de amonio pH 6 y 1mCi de ¹⁷⁷LuCl₃ (Ae= 6,36, 7,52 y 9,73 Ci/mg), a 80°C, durante 30 min, a pH 5,5. La estabilidad in-vitro se estudió incubando 2.5 µg ¹⁷⁷Lu-DOTA-MG y 500 µl de suero humano, a 37°C, durante 15 min, utilizando cromatografía líquida de alta performance, de fase reversa. Se realizaron

biodistribuciones en ratones normales a 15 y 30 min, 1 y 4 h p.i. Se calcularon las dosis absorbidas para los diferentes órganos del ratón por unidad de actividad inyectada del radiofármaco (cGy/ μ Ci) mediante el esquema MIRD. Se extrapolaron los resultados obtenidos a un modelo humano empleando los métodos de escalación por tiempo (A) y extrapolación directa (B) y se calcularon las máximas dosis tolerables en función de los órganos críticos (mCi/kg).

Resultados: Empleando el $^{177}\text{LuCl}_3$ de $A_e = 6,36, 7,52$ y $9,73$ Ci/mg se marcaron 20 μ g de péptido con una PR de 98,0 %, 97,5% y 99,0 %, respectivamente. Las biodistribuciones, mostraron rápida depuración sanguínea 1,5% DI/g a 30 min p.i y excreción renal 9,44 y 2,31 % DI/g a 30 min y 4 h p.i, respectivamente. La estabilidad en suero mostró, en el perfil cromatográfico, un segundo pico con un tiempo de retención inferior al péptido marcado, correspondiente a una especie oxidada del péptido en el aminoácido metionina (22,2% a los 15 min y 68,9% para un estudio realizado 24 hs después). El órgano que recibe la mayor dosis es el riñón con un valor de 2,06 y 2,51 cGy/mCi para el hombre y la mujer adultos, respectivamente. Esto es consistente con datos obtenidos en pacientes para el ^{177}Lu -DOTA-TATE (3,7- 8,14 cGy/mCi). La máxima actividad tolerable de ^{177}Lu -DOTA-MG que puede ser inyectada sin producir toxicidad en riñones es de 13,2 mCi/kg y 14 mCi/kg, para el hombre y la mujer adultos, respectivamente (método A) y de 37 mCi/kg y 44,1 mCi/Kg (método B).

Conclusiones: Hasta el momento, se pudo obtener ^{177}Lu -DOTA-MG con $A_e = 0,05$ mCi/ μ g de péptido. Los resultados de extrapolación a un modelo humano que mejor se ajustan a los datos de pacientes son los del método de escalación por tiempo. Con estos resultados se concluyó con la parte dosimétrica de la etapa de ensayos preclínicos.

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Tratamiento de tumores neuroendocrinos (TNE) con péptidos análogos de la somatostatina marcados con radionucleidos

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Purpose: Advanced NETs have little response to radiotherapy or chemotherapy, systemic treatment with radioactive SST analogous is a promissory tool in its treatment. We present our pioneering experience in Latin America using analogous of SST labeled either with ^{90}Y or ^{177}Lu . Materials: We evaluated 40 patients (50.3 years, range 12-74) with histological proved NET and SST receptors over-expression demonstrated by SPECT or PET/CT images with ^{111}In -DOTATOC or ^{68}Ga -DOTATATE. We evaluated clinical response, laboratory test, images with ^{111}In -DOTATATE, ^{90}Y , ^{177}Lu , and ^{68}Ga -DOTATATE PET/CT or CT. Results: We observed progression of disease in 10 (7,5%), partial remission in 25 (62,5%), stable disease in 3 (7,5%) and complete remission

in 2 (5,0%). There was little toxicity without significant renal deterioration. We observed tumor mass reduction and improvement of quality of life in most of the patients. Conclusion: The therapy with radiopeptides is a safe and effective procedure in the treatment of advanced TNA

Propósito: Los TNE avanzados tienen escasa respuesta a radioterapia o quimioterapia, el tratamiento sistémico con análogos de la SST radiactivos es una herramienta promisoriosa en su tratamiento. Presentamos nuestra experiencia, pionera en Latinoamérica, utilizando análogos de SST marcados con ^{90}Y ó ^{177}Lu . Material: Evaluamos 40 pacientes (50.3 años, rango 12-74) con TNE confirmados histológicamente y sobre-expresión de receptores de SST demostrada mediante imágenes. SPECT (^{111}In -DOTATOC) ó PET/CT (^{68}Ga -DOTATATE). Se evaluó respuesta clínica, laboratorio, imágenes con ^{111}In -DOTATATE, post-terapia con ^{90}Y ó ^{177}Lu , ^{68}Ga -DOTATATE PET/CT o TAC.

Resultados: Observamos progresión de enfermedad en 10 (25.0%), remisión parcial en 25 (62.5%), enfermedad estable en 3 (7.5%) y remisión completa en 2 (5.0%). Hubo escasa toxicidad sin deterioro renal significativo. Observamos reducción tumoral y mejoría de calidad de vida en la mayoría de los pacientes. Conclusión: La terapia con radiopéptidos es un procedimiento seguro y efectivo en el tratamiento de TNA avanzados.

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Effectiveness of treatment of gastroenteropancreatic non-functioning neuroendocrine tumours consisted of Sandostatin LAR® after ^{90}Y - and/or ^{177}Lu - DOTA-TATE therapy.

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The aim of the study: Assessment of treatment with 'cold' somatostatine analog (SA) – octreotide after 'SA hot': ^{90}Y -and/or ^{177}Lu - DOTA-TATE as somatostatine receptor radiotherapy (SRRT) of gastroenteropancreatic neuroendocrine tumors (GEP NET). Sandostatin LAR® is a prolonged release formulation of SA – octreotide, an octapeptide which binds to the somatostatin receptor subtype 2 (SSTR2) with higher, and to subtype 5 (SSTR5) with lower affinity. ^{90}Y - and ^{177}Lu - DOTA-TATE are radiopharmaceuticals consisted of β (-) emitter $^{90}\text{yttrium}$ or $^{177}\text{lutetium}$ triggered with SA – octreotate which binds to the same SSTRs. Materials and methods: 4 patients with histopathological confirmed non-functioning GEP-NET were included to the study. The first and second patient with pancreatic NET with metastases to the liver, the third patient with large intestinal NET and metastases to the paraaortic lymph nodes and to the liver, the fourth patient with liver metastases and unknown primary origin of NET. The presence of somatostatin receptors in all GEP-NETs was confirmed in Somatostatine Receptor Scintigraphy (SRS) with $^{99\text{mTc}}$ -HYNIC-TATE before treatment. All radiopharmaceuticals were produced by POLATOM – Swierk/Poland. The first patient was treated four times with

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90Y-DOTA-TATE and two times with 177Lu- DOTA-TATE, the second and third patients were treated four times with 90Y-DOTA-TATE and the fourth patient was treated four times with 177Lu- DOTA-TATE. Each dose of 90Y-DOTA-TATE was 3,7GBq and 177Lu- DOTA-TATE was 7,4 GBq given at 4- 8 weeks intervals. After such a course with radiopharmaceuticals all of the patients were treated with Sandostatin LAR® in dose of 20 mg per month. Control SRS (SPECT/CT) were performed after 3 - 4 months of the last dose of radiopreparation and the second time after further 12 months treatment with Sandostatin LAR®. The level of chromogranin A (CgA) was estimated before and after treatment with radiopreparations and after 'cold' somatostatin analog therapy. The local ethical committee approval has been obtained before the study. Results: On the base of SRS, in all of patients stabilization of disease was reached both after somatostatin receptor radiotherapy (SRRT) and 1 year Sandostatin LAR® treatment. In the beginning the first pts had chromogranin A (CgA) level – 1293,06 ng/ml, second – 338,7 ng/ml, third - 38,5 ng/ml, fourth - 213,2 ng/ml. After SRRT the first patient had CgA level 670,06 ng/ml, the second – 295,9 ng/ml, the third - 251,4 ng/ml, the fourth - 346,2 ng/ml. After further 12 months of Sandostatine LAR treatment CgA level was: in the first patient 259,49 ng/ml, in the second – 149,88 ng/ml, in the third - 183,3 ng/ml, in the fourth - 196,3 ng/ml Conclusion: Somatostatin receptor radiotherapy and further octreotide (Sandostatin LAR®) seems to be useful in treatment of non- functioning gastroenteropancreatic neuroendocrine tumours.

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Peptide receptor radionuclide therapy in neuroendocrine tumors: preliminary results in 18 cases treated with 90Y-DOTATOC

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Background: Peptide receptor radionuclide therapy (PRRT) is a significant development in the field of therapeutic Nuclear Medicine which is particularly applicable to neuroendocrine tumours that over express somatostatin receptors. Several phase I and phase II studies done over the past few years have reported optimistic results of varying degrees with PRRT using either 90Y-DOTATOC and/or 177Lu-DOTATATE in neuroendocrine tumours. Aim: The aim of this study is to relate preliminary experience obtained with the use of 90Y-DOTATOC in the treatment of patients with somatostatin receptor positive tumours. Patients and Method: Eighteen patients with progressive metastatic neuroendocrine tumors were included in the study. Before therapy with 90Y-DOTATOC, the patients underwent staging with CT followed by 111In-Octreoscan to document the intensity of somatostatin receptors in the tumours. Among the inclusion criteria, a life expectancy of 6 months and absence of other neoplasms were ascertained. The radiolabeled somatostatin analogue 90Y-DOTATOC was produced on-site in the

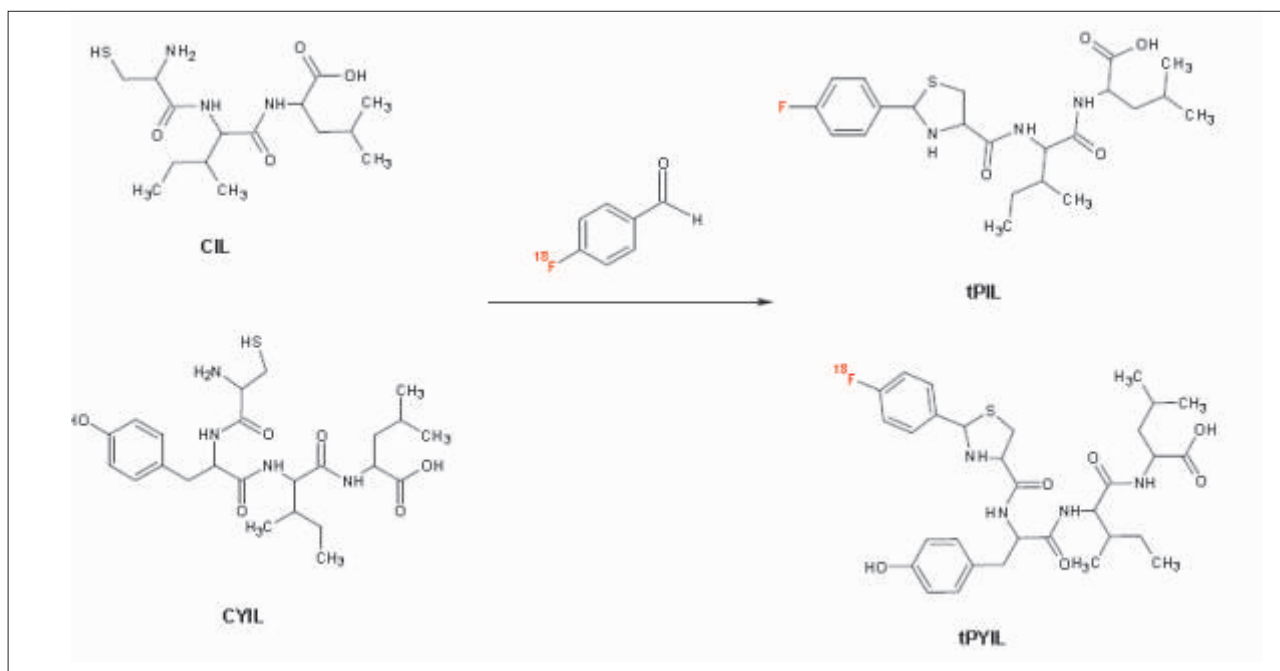
radiochemistry department of the Civic Hospital starting from the two precursors 90Y-clorurate and DOTA-Tyr3-Octreotide (DOTA-Toc) (GMP-Grade). All patients were hospitalized for at least 3 days for each treatment sessions, in accordance with the legal requirements for radioactivity control. Amino acid infusion was given both before and after the administration of a fixed activity of 2.56 GBq of 90Y-DOTATOC which was repeated at an interval of 8 weeks. Patients were assessed by serial CT examination at one month each after the second and fourth cycle of therapy to document regression and/or progression of tumour growth. For evaluation of response, WHO standard criteria were used. Blood counts and chemistry, chromagranin A measurement and tumor-specific hormonal examinations were additional parts of the evaluation protocol. In addition, octreoscan was also performed for restaging. In cases of progressive disease (PD), treatment with 90Y-DOTATOC was withdrawn. For patients with evidence of stable disease (SD) or partial response (PR) defined by CT and 111In-Octreoscan, treatment with 90Y-DOTATOC was continued for a further 1-2 cycles. Brehmstrahlung SPET imaging was done in some patients to assess 90Y-DOTATOC uptake in the tumours. Results: Eighteen patients (13 male and 5 female) with age range 18-75 years underwent therapy with 90Y-DOTATOC. There were twelve patients with neuroendocrine gastroenteropancreatic tumors (GEP-NET), three patients with unknown primary site, two patients with medullary thyroid carcinoma and one patient with breast cancer. Prior to 90Y-DOTATOC therapy, nine patients had been treated with cold somatostatin analogues, one patient had external beam radiotherapy, one patient had chemotherapy and one had 131I-MIBG therapy. Six patients with very advanced disease and grade I in one patient. Mild renal toxicity in the form of reversible elevation of serum creatinine was observed in two patients. Conclusion: The study showed 90Y-DOTATOC to be a safe and effective treatment option in patients with advanced somatostatin receptor positive tumours with a good objective response rate.

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Preparation of [18F] containing neurotensine-derived peptides

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Labelling was realized by way of a thiazolidine ring forming reaction between a N-terminal Cys-residue and 4-[18F]-fluorobenzaldehyde (this type of reaction has been mainly used for building up larger molecules from components by chemical ligation, but never for radiolabeling of peptides[1]). The 4-[18F] fluorobenzaldehyde was synthesized from 4-formyl-phenyltrimethylammonium triflate according to literature methods in a TracerLab Fx/FN module: the SNAr reaction was performed in DMF solution at 120 °C during 20 mins, the reaction mixture was diluted with 0,05 M HCl and pressed through serially connected MN PS-H and SepPak C18 Plus cartridges and subsequently washed with water. After removing the cation exchanger, the fluorobenzal-dehyde is eluted with methanol. This raw product is either further



purified by prep HPLC (SphereClone 5 μ ODS 2 column, 45 % ethanol as eluent, serially coupled UV and gamma detectors) and isolated by SPE on SepPak C18Plus cartridge and eluted with ether. However, the raw product in MeOH is pure enough to be used in the thiaproline forming reaction. 0,5 ml of the ethereal or methanol solution of [18F]fluorobenzaldehyde is combined with the peptide containing a N-terminal Cys-residue (0,4-1 mg CYIL or CIL in 250 μ l 0,1 M aqueous natriumacetate buffer pH 4,5) and kept at 80 $^{\circ}$ C in a closed vessel for 30 min (the radiochemical yield is 70 -98 %, as evidenced by HPLC). The formed 2-(4-[18F]fluorophenyl)- thiaproline-Isoleucyl-leucine or -tyrosinyl-Isoleucyl-leucine has been separated by prep HPLC followed by SPE on C18Plus SepPak. The purified compound was eluted either with ethanol or DMSO, and can be further diluted with phys saline. Alternatively, the HPLC fraction was collected in a flask containing 50 ml water and loaded onto a Waters QMA light cartridge (pretreated in the usual way) that was washed with water and the peptide derivative eluted with 70 mM NaH₂PO₄ solution. [The product's radiochromatogram always contains a small peak (1-2 %) of fluorobenzaldehyde perhaps due to the equilibrium between the ring and its components. Nevertheless, the compound is unchanged in neutral solutions for at least 2 hrs at RT]. Radiochem. Yield (%) Spec. Activity (Gbg/ μ mol) tPYIL 3 - 50 6 - 33 tPIL 2 - 28 The chemical purity of the labeled peptides is 90- 98 %.

Reference

1. Lemieux, G.A. and Bertozzi, C.R.: TIBTECH 1998, 16, 506-513 and refs cited

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I-131 MIBG imaging in the diagnosis of pheochromocytoma: 'Philippine setting'

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The clinical diagnosis of pheochromocytoma is easy, considering that it manifests as labile hypertension, attacks of palpitations, headache, sweating, pallor or flushing. Urinary VMA or metanephrines seem to be the first investigative step as well as a CT scan to localize it as 85-90% arise from the adrenal medulla. Ten percent of these tumors are bilateral but non-adrenal tumors may arise from the sympathetic ganglia, usually alongside the aorta or its branches and in the wall of the urinary bladder. One percent is found outside the abdominal cavity. Meta-iodobenzyl guanidine (MIBG) is an excellent scanning agent that is taken up by most benign and malignant pheochromocytoma tissues. While this procedure is quite costly and underutilized in the Philippines, this paper was done to review its indications and how helpful it can be. From 2001-2005, I131 MIBG scintigraphy was done only in 17 patients in two medical centers to confirm the diagnosis of pheochromocytoma. The clinicians must be informed that this is not a screening procedure but it is particularly helpful in surveying the entire body for adrenal and extra-adrenal metastatic lesions. It is also diagnostic of intra-adrenal paragangliomas, neuroblastoma, carcinoids, and medullary thyroid carcinoma. This study was, likewise, done with the thought that MIBG may be utilized in the future for therapy as it has shown to be effective in pheochromocytoma and neuroblastoma.