GEP–NETs UPDATE

Radionuclide therapy in neuroendocrine tumors

Wouter A van der Zwan, Lisa Bodei1, Jan Mueller-Brand2, Wouter W de Herder, Larry K Kvols3 and Dik J Kwekkeboom

Department of Nuclear Medicine, Erasmus MC, University Medical Center, s-Gravendijkwal 230, 3015CE Rotterdam, The Netherlands, 1Department of Nuclear Medicine, European Institute of Oncology, Milan, Italy, 2Department of Nuclear Medicine, University Hospital Basel, Basel, Switzerland and 3Department of GI Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida, USA

Abstract

Peptide receptor radionuclide therapy (PRRT) is a promising new treatment modality for inoperable or metastasized gastroenteropancreatic neuroendocrine tumors (GEPNETs) patients. Most studies report objective response rates in 15–35% of patients. Also, outcome in terms of progression free survival (PFS) and overall survival compares very favorably with that for somatostatin analogs, chemotherapy, or new, ‘targeted’ therapies. They also compare favorably to PFS data for liver-directed therapies. Two decades after the introduction of PRRT, there is a growing need for randomized controlled trials comparing PRRT to ‘standard’ treatment, that is treatment with agents that have proven benefit when tested in randomized trials. Combining PRRT with liver-directed therapies or with targeted therapies could improve treatment results. The question to be answered, however, is whether a combination of therapies performed within a limited time-span from one another results in a better PFS than a strategy in which other therapies are reserved until after (renewed) tumor progression. Randomized clinical trials comparing PRRT with other treatment modalities should be undertaken to determine the best treatment options and treatment sequelae for patients with GEPNETs.

Invited Authors’ profiles:
Dik Kwekkeboom, MD works for the Department of Nuclear Medicine at the University Hospital, Erasmus MC, Rotterdam, The Netherlands. His major research interest is peptide receptor imaging and he coordinates the studies on therapy with the radiolabelled somatin analog 177Lu-octreotate in patients with neuroendocrine tumors. He has numerous publications in international journals and textbooks, mainly in the field of endocrinology and peptide receptor scintigraphy and therapy.

Wouter A van der Zwan currently works as research physician within the peptide receptor radionuclide therapy (PRRT) team at the Department of Nuclear Medicine of the Erasmus MC, Rotterdam and is directly involved in the treatment of patients affected by a Neuroendocrine Tumor with PRRT. Besides the clinical care of patients undergoing PRRT, his work includes conducting scientific research on the early and late effects, and optimization of PRRT.
Introduction

The majority of gastroenteropancreatic neuroendocrine tumors (GEPNETs) express somatostatin receptors and can be treated with radiolabeled somatostatin analogs. The majority of patients that have been treated with this so-called peptide receptor radionuclide therapy (PRRT) had inoperable metastatic disease, and 70–90% of them had liver metastases (1, 2, 3, 4, 5).

PRRT: efficacy

Because at that time somatostatin analogs labeled with β-emitting radionuclides were not available for clinical use, early studies in the 1990s used high activities of the Auger electron emitting [111In-DTPA0]octreotide (111In-octreotide) for PRRT. These treatments often resulted in symptom relief in patients with metastasized neuroendocrine tumors (NETs), but objective tumor responses were rare (Table 1) (6, 7).

The next generation of analogs used in PRRT consisted of a modified somatostatin analog, [Tyr3]octreotide, and a different chelator, DOTA instead of DTPA, which allows stable binding of the β-emitting radionuclide 90Yttrium (90Y). Its maximal tissue penetration is 12 mm and its half life is 2.7 days. [90Y-DOTA0,Tyr3]octreotide ([90Y-DOTATOC]) was used in several phase-1 and phase-2 PRRT trials in various countries (Table 1). The registered objective responses range from 4 to 33%. Differences in cycle doses and administered cumulative dose, as well as differences in patient characteristics (included tumor types, patient performance status), make it virtually impossible to compare these studies. Different studies report median progression-free survival (PFS) varying from 17 to 29 months, and median overall survival (OS) from 22 to 37 months (Table 2) (1, 2, 3, 4, 5). In a recent report on the treatment effects of 90Y-DOTATOC in a large group of patients, the response to 90Y-DOTATOC was associated with longer survival (8).

177Lutetium (177Lu) is a medium energy β-emitter, with a maximal tissue penetration of 2 mm. 177Lu also emits low-energy γ-rays, allowing scintigraphy and subsequent dosimetry using the same, therapeutic, compound. The somatostatin analog [DOTA0,Tyr3]octreotate differs from [DOTA0,Tyr3]octreotide only in that the C-terminal threoninol is replaced with threonine, resulting in a higher affinity for the somatostatin receptor subtype 2 than octreotide (9). The treatment effects of [177Lu-DOTA0,Tyr3]octreotate (177Lu-octreotate) therapy were described in a large group of GEPNETs patients (5). Complete response (CR) was found in five (2%) patients, partial response (PR) in 86 (28%), and minor response (MR) in 51 (16%) patients (Table 2). Prognostic factors for predicting tumor response (CR, PR, or MR) as treatment outcome were high uptake on the Octreoscan, Karnofsky performance score >70, and low metastatic load to the liver. Median time to progression was 40 months from start of treatment. Progression of disease was more common in patients with an extensive disease or in a poor general clinical condition (Karnofsky score <70%, significant weight loss, the presence of bone metastases). Several of these factors that had a significant impact on PFS were also found in another study (10). Median OS was 46 months (Table 2). It may be postulated that

Table 1 Tumor responses in patients with gastroenteropancreatic neuroendocrine tumors, treated with different radiolabeled somatostatin analogs.

<table>
<thead>
<tr>
<th>Center (reference)</th>
<th>Ligand</th>
<th>n</th>
<th>CR</th>
<th>PR</th>
<th>MR</th>
<th>SD</th>
<th>PD</th>
<th>CR + PR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotterdam (6)</td>
<td>[111In-DTPA0]octreotide</td>
<td>26</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>11</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>New Orleans (7)</td>
<td>[111In-DTPA0]octreotide</td>
<td>26</td>
<td>0</td>
<td>2  (8%)</td>
<td>NA</td>
<td>21</td>
<td>81</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Milan (13)</td>
<td>[90Y-DOTA0,Tyr3]octreotide</td>
<td>21</td>
<td>0</td>
<td>6  (29%)</td>
<td>NA</td>
<td>11</td>
<td>52</td>
<td>4 (19%)</td>
</tr>
<tr>
<td>Basel (14, 15, 41)</td>
<td>[90Y-DOTA0,Tyr3]octreotide</td>
<td>74</td>
<td>3  (4%)</td>
<td>15</td>
<td>20 (%)</td>
<td>NA</td>
<td>48</td>
<td>65</td>
</tr>
<tr>
<td>Basel (15, 41)</td>
<td>[90Y-DOTA0,Tyr3]octreotide</td>
<td>33</td>
<td>2  (6%)</td>
<td>9</td>
<td>27 (%)</td>
<td>NA</td>
<td>19</td>
<td>57</td>
</tr>
<tr>
<td>Multicenter (1)</td>
<td>[90Y-DOTA0,Tyr3]octreotide</td>
<td>58</td>
<td>0</td>
<td>5</td>
<td>9  (12%)</td>
<td>NA</td>
<td>33</td>
<td>61</td>
</tr>
<tr>
<td>Multicenter (2)</td>
<td>[90Y-DOTA0,Tyr3]octreotide</td>
<td>90</td>
<td>0</td>
<td>4</td>
<td>4  (4%)</td>
<td>NA</td>
<td>63</td>
<td>70</td>
</tr>
<tr>
<td>Copenhagen (3)</td>
<td>[90Y-DOTA0,Tyr3]octreotide</td>
<td>53</td>
<td>2  (4%)</td>
<td>10</td>
<td>19 (%)</td>
<td>NA</td>
<td>34</td>
<td>64</td>
</tr>
<tr>
<td>Warsaw (4)</td>
<td>[90Y-DOTA0,Tyr3]octreotide</td>
<td>58</td>
<td>0</td>
<td>13</td>
<td>23 (%)</td>
<td>NA</td>
<td>44</td>
<td>73</td>
</tr>
<tr>
<td>Rotterdam (5)</td>
<td>[177Lu-DOTA0,Tyr3]octreotate</td>
<td>310</td>
<td>5  (2%)</td>
<td>86</td>
<td>28 (%)</td>
<td>51</td>
<td>16 (%)</td>
<td>107</td>
</tr>
<tr>
<td>Gothenburg (42)</td>
<td>[177Lu-DOTA0,Tyr3]octreotate</td>
<td>26</td>
<td>0</td>
<td>6  (38%)</td>
<td>NA</td>
<td>8</td>
<td>50</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Lund (43)</td>
<td>[177Lu-DOTA0,Tyr3]octreotate</td>
<td>12</td>
<td>0</td>
<td>2  (17%)</td>
<td>3</td>
<td>25 (%)</td>
<td>5</td>
<td>40</td>
</tr>
<tr>
<td>Milan (10)</td>
<td>[177Lu-DOTA0,Tyr3]octreotate</td>
<td>42</td>
<td>1  (2%)</td>
<td>12</td>
<td>29 (%)</td>
<td>9</td>
<td>21 (%)</td>
<td>11</td>
</tr>
</tbody>
</table>

CR, complete response; PR, partial response; MR, minor response; SD, stable disease; PD, progressive disease.
early treatment with PRRT can increase the PFS and OS. However, in a retrospective series of 68 patients suffering from advanced pNET, 35 patients received PRRT as first-line treatment. The outcome regarding PFS and OS did not differ from patients treated with PRRT in a later setting (11).

In a large group of (nearly 300) patients treated with PRRT and who had a long follow-up, it was shown that quality of life (QoL) and also symptomatology improved in 40–70% of cases, depending on the preexistence of a certain symptom (12). This is important because the months to years that are gained after PRRT can only be called promising if the time that is gained is free of serious side-effects or symptomatology that affect QoL. By contrast, it was shown that the years gained after PRRT show an improved QoL, as judged by the patients themselves, according to a validated questionnaire (12).

**PRRT: side-effects**

PRRT is generally well tolerated. Acute side-effects are usually mild and self-limiting. Nausea or, more rarely, vomiting is related to the concomitant administration of nephro-protective amino acids. Other, more subacute side-effects are related to the radiopeptide itself, such as fatigue, hematologic or renal toxicity, mild hair loss (observed with $^{177}$Lu-octreotate), impairment of male fertility or, more rarely, an exacerbation of a clinical syndrome. The most common subacute side-effect of PRRT, occurring within 4–6 weeks after therapy, is hematologic toxicity. Hematologic toxicity is caused by irradiation of the bone marrow. Usually hematologic toxicity is mild and reversible. More serious, WHO grade 3 or 4 toxicity may occur in <15% of patients (1, 3, 8, 10, 13, 14, 15, 16).

Long-term serious side-effects of PRRT are renal failure or myelodysplastic syndrome (MDS)/leukemia (Table 3). Proper kidney protection, with the co-infusion of positively charged amino acids, is mandatory in PRRT. With advances in expertise and knowledge about PRRT, cases of severe, end-stage, renal damage are currently very rare. However, despite kidney protection, loss of kidney function can occur after PRRT, with a creatinine clearance loss of about 3.8% per year for $^{177}$Lu-octreotate and 7.3% per year for $^{90}$Y-DOTATOC (17). Studies have demonstrated that a higher and more persistent decline in creatinine clearance is more frequent if risk factors for delayed renal toxicity are present, particularly long-standing and poorly controlled diabetes and hypertension (18).

**Table 3** Long-term toxicity in patients with neuroendocrine tumors, treated with different radiolabeled somatostatin analogs.

<table>
<thead>
<tr>
<th>Center (reference)</th>
<th>Ligand</th>
<th>n</th>
<th>FU</th>
<th>Toxicity</th>
<th>MDS</th>
<th>Leukemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milan (13)</td>
<td>$^{90}$Y-DOTA$_5$,Tyr$_3$octreotide</td>
<td>40</td>
<td>19</td>
<td>10% Grade 1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Basel (14)</td>
<td>$^{90}$Y-DOTA$_5$,Tyr$_3$octreotide</td>
<td>41</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Basel (15, 41)</td>
<td>$^{90}$Y-DOTA$_5$,Tyr$_3$octreotide</td>
<td>39</td>
<td>6</td>
<td>3% Grade 2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Multicenter (1)</td>
<td>$^{90}$Y-DOTA$_5$,Tyr$_3$octreotide</td>
<td>58</td>
<td>18</td>
<td>3% Grade 4</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Basel (16)</td>
<td>$^{90}$Y-DOTA$_5$,Tyr$_3$octreotide</td>
<td>31</td>
<td>12</td>
<td>12.9% Grade 3/4$^a$</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Copenhagen (3)</td>
<td>$^{90}$Y-DOTA$_5$,Tyr$_3$octreotide</td>
<td>53</td>
<td>17</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Basel (8)</td>
<td>$^{90}$Y-DOTA$_5$,Tyr$_3$octreotide</td>
<td>1109</td>
<td>23</td>
<td>9.2% Grade 3/4$^a$</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Rotterdam (5)</td>
<td>$^{177}$Lu-DOTA$_5$,Tyr$_3$octreotate</td>
<td>504</td>
<td>19</td>
<td>0.4% Grade 4</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Milan (10)</td>
<td>$^{177}$Lu-DOTA$_5$,Tyr$_3$octreotate</td>
<td>51</td>
<td>29</td>
<td>24% Grade 1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

FU, follow-up; MDS, myelodysplastic syndrome. Grades pertain to World Health Organization (WHO) classification. $^a$Toxicity based on glomerular filtration rate.
With adequate renal amino acid protection, grade 3–4 renal toxicity occurs in <3% of patients (Table 3). One recent study, however, states a grade 3–4 renal toxicity in 9% of their patients (8). This relatively high incidence could be related to relatively high activities administered per cycle and to the fact that patients with pre-existing reduced kidney function were not excluded from treatment. The possible lack of use of amino acids in the first years of this study must also be taken into account (19).

Serious side-effects of PRRT on the bone marrow, such as MDS or leukemia, have been reported by various groups. An exact measure of these events is frequently hampered by their occurrence in heavily pretreated patients and the short follow-up of the patients. These events are rare and the causal relationship with PRRT may be controversial, because of the previous treatments, such as chemotherapy or radiotherapy. Their frequency seems higher after 177Lu-octreotate than after 90Y-DOTATOC, but also in analyses with long patient follow-up, their frequency does not exceed 2% of patients (D J Kwekkeboom, unpublished observation).

**PRRT: variants**

Over the last years, there have been a number of attempts to improve PRRT using different approaches.

From experiments in rats, it became clear that 90Y-labeled somatostatin analogs may be more effective for larger tumors, and 177Lu-labeled somatostatin analogs may be more effective for smaller tumors, while their combination may be the most effective (20). Several retrospective, non-randomized patient studies seem to indicate the same (21, 22, 23). A recent follow-up report on the efficacy of the combination of PRRT Seregni et al. (22, 24) reported an objective response rate in 43% of the cases, whereas in their initial report an objective response rate of 67% was found. Prospective, randomized controlled studies are needed to ultimately prove that PFS is better when using a combination of radionuclides.

Several groups have investigated the feasibility of locoregional, i.e. intraarterial, administration of radio-labeled somatostatin analogs (25, 26, 27, 28). It results in a higher uptake of radioactivity in liver metastases and tumor response rates seem higher than with i.v. administration. Long-term responses and toxicity are not available yet.

The application of radiosensitizing chemotherapeutic agents in the treatment of tumors with external beam irradiation may lead to increased anti-tumoral efficacy and another way to improve PRRT. After proving the safety of the combined therapy of 5-fluorouracil (5-FU) and PRRT, a randomized trial was started comparing treatment with 177Lu-octreotate with and without capecitabine (the oral prodrug of 5-FU) (Xeloda; Roche) in patients with GEPNETs (29). Results of another non-randomized phase II study treating patients with a combination of capecitabine and 177Lu-octreotate demonstrated tumor control and stabilization in 94% of the 33 included patients. However, due to grade 3 capecitabine-induced angina, three patients discontinued the drug, but were able to complete the intended four cycles of PRRT (30). Feasible results were also published for the combination of capecitabine and 90Y radioimmunotherapy and 111In-octreotide radiopeptide therapy (31, 32). The use of radiosensitizing agents is, therefore, not limited to the combination of one specific type of radionuclide.

New applications of PRRT may include the neoadjuvant use of PRRT for pancreatic NETs. A few case reports have described the neoadjuvant use of PRRT in patients with pancreatic NETs who could be operated on successfully after PRRT (33, 34). As surgery is the only curative option for patients with GEPNETs, this neoadjuvant treatment is very promising.

PRRT may also be used in an adjuvant setting after surgery of GEPNETs, preventing tumor development after spread due to manipulation of the tumor during surgery or preventing further growth of already present micrometastases. In an animal study, therapy with 177Lu-octreotate prevented or significantly reduced the growth of tumor deposits in the liver after injection of tumor cells via the portal vein mimicking preoperative tumor spill (35). To detect a difference in survival and/or tumor recurrence rate in patients treated with and without adjuvant PRRT, a large, multicenter trial with years of follow-up would be needed.

**PRRT as salvage therapy**

Although tumor response rates after initial treatment with PRRT are encouraging, CR is rare and eventually the residual tumor(s) will progress again. Retreatment with extra cycles of PRRT as salvage therapy may be considered when better alternatives are not available. It has been reported that ‘salvage’ therapy with two additional cycles of 177Lu-octreotate does not lead to serious hematological or nephrotoxic side-effects. However, the tumor response rate was lower compared with initial treatment (36). It seems that long-lasting PFS after the initial treatment with PRRT also predicts a prolonged PFS after salvage therapy (37).
Discussion

PRRT is a promising new treatment modality for inoperable or metastasized GEPNET patients (Fig. 1). Complete and partial responses obtained after treatment with \(^{90}\text{Y}\)-DOTATOC are in the same range as after treatment with \(^{177}\text{Lu}\)-octreotate.

Most studies report objective response rates in 20–35% of patients. Also, outcome in terms of PFS and OS (from 16 to 33 months, and from 22 to 46 months, respectively) compares very favorably with that for somatostatin analogs, chemotherapy, or new, ‘targeted’ therapies. They also compare favorably to PFS data for liver-directed therapies, i.e. embolization, chemoembolization, or treatment with \(^{90}\text{Y}\)-labelled microspheres. However, several facts that may invalidate such comparisons should be considered: i) the patient populations that undergo liver-directed therapies or PRRT may be different (for instance patients who had Whipple-procedures are excluded from the first, whereas patients who have somatostatin-receptor-negative tumors are excluded from the second); and ii) the results for PRRT pertain to patients with limited as well as extensive liver involvement. From multivariate analysis, it is known that patients extensive liver involvement perform worse (5, 10). However, however, be assumed that in patients with predominant liver disease, PRRT performs better in terms of PFS than liver-directed therapies.

There is a need for randomized controlled trials comparing PRRT to ‘standard’ treatment, that is treatment

---

**Figure 1**

Example of partial response after four cycles of \(^{177}\text{Lu-DOTA}\text{O}^6\text{Tyr}^3\) octreotate (cumulative dose of 29.6 GBq) in a patient with a metastasized pancreatic neuroendocrine tumor. (A) Upper row: baseline CT scan demonstrated a mass within the pancreatic body with diffuse liver metastases. CT scans after treatment again demonstrated multiple liver metastases and the pancreatic mass. However, the lesions clearly diminished in size and some disappeared. Lower row: planar scintigraphy performed 24-h post-injection demonstrated intense uptake by the receptor-positive liver metastases and the pancreatic mass. During consecutive treatment cycles, less tumor mass was observed indicating tumor response. (B) Plot depicts serum chromogranine A (CgA) concentrations at baseline, 6 weeks after each administration of PRRT (Post-PRRT) and during follow-up. Owing to a radiation-induced inflammatory reaction of tumor tissue, an increase in CgA levels was observed in response to PRRT.
with agents that have proven benefit when tested in randomized trials (Sandostatin LAR in metastatic midgut carcinoids and everolimus and sunitinib in inoperable and/or metastatic pancreatic NETs). The same holds for liver-directed therapies. A randomized study comparing PRRT with 177Lu-octreotate to high-dose Sandostatin LAR treatment in patients with progressive metastatic midgut carcinoids was recently started in Europe and the USA. A study comparing PRRT to sunitinib or everolimus in patients with pancreatic NETs is expected to follow soon.

Recently, the results of new targeted therapies for the treatment of GEPNETs have been presented. Treatment with sunitinib (Sutent; Pfizer, Inc., New York, NY, USA), a tyrosine kinase inhibitor, resulted in a longer median PFS than placebo (11 vs 5 months) in patients with pancreatic NETs (38). Also, treatment with everolimus (Afinitor; Novartis Pharmaceuticals), an inhibitor of mammalian target of rapamycin (mTOR), resulted in a longer median PFS than placebo (11 vs 5 months) in patients with pancreatic NETs (39). The combination of PRRT with sunitinib or everolimus, or the sequential use of PRRT with one of these compounds, may be of interest in the treatment of patients with pancreatic NETs.

The next question to be addressed is then, whether combining PRRT with liver-directed therapies, or, for that matter, with targeted therapies, such as treatment with everolimus or sunitinib, could improve treatment results in terms of percentage objective responses, or, preferentially, PFS and OS. The results of such an approach in a sequential setting, i.e. 90Y-microsphere treatment after failure to or reprogression after PRRT, were recently published and hold great promise (40). The question to be answered, however, is whether a combination of PRRT and liver-directed therapy performed within a limited time-span from one another (for instance 3–4 months) results in a better PFS than a strategy in which liver-directed therapy is reserved until after (renewed) tumor progression. This same question can be asked for the combination of PRRT with chemotherapy with, for instance, temozolomide and capecitabine or with everolimus or sunitinib. Such combinations, in our view, are promising only of their result in a longer PFS/OS than when using a sequential approach, in which the second treatment is only started if the disease progresses after the first. A higher percentage of objective responses with a combinatorial approach may not be mistaken for a better treatment outcome, because with any of the two single treatments, a certain percentage of patients can be expected to have an objective response anyhow, and the added responses will always exceed the response of any single treatment. Also, it was shown in a large multivariate analysis that tumor response other than progressive disease did not result in significant differences in PFS or OS (i.e. patients with PR had no longer PFS than those with stable disease) (5). It should also be kept in mind that in the vast majority of patients, the goal of treatment is not cure, but prevention of disease progression. With a limited number of treatment options, combining treatment modalities at the beginning may leave the attending physician empty-handed later on.

**Conclusions**

PRRT is a new and valuable treatment modality for patients with inoperable or metastasized GEPNETs. PRRT is generally well tolerated and acute side-effects are usually mild and self-limiting. Most studies report rates of 15–35% in terms of objective response rates. In terms of PFS and OS, PRRT compares favorably to registered pharmaceutical and liver-directed therapies. Combining PRRT with radiosensitizing chemotherapeutical agents or combining 90Y and 177Lu as tandem-treatment may improve the anti-tumoral efficacy. Another way to improve uptake of the radiopharmaceutical is by intraarterial administration in case of high tumor load in the liver. Randomized clinical trials comparing PRRT with other treatment modalities should be undertaken to determine the best treatment options and treatment sequelae for patients with GEPNETs.

**Declaration of interest**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

**Funding**

This review did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

**Author contribution statement**

All authors have read this final version of the manuscript and have agreed with its present form. All authors contributed equally. The enclosed manuscript has not been submitted to any other journal.

**References**


Received 16 June 2014
Revised version received 29 July 2014
Accepted 12 August 2014