Review of Pharmacoeconomic Studies in Radionuclide Therapy of Painful Bone Metastases

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Abstract: By virtue of the rapid development of nuclear medicine technologies, pharmacoeconomics shall occupy one of the key roles in assessing the applicability of one or another nuclear medicine’s methods in clinical practice. Based on existing evidence, application of the $^{153}$Sm-EDTMP and $^{89}$SrCl$_2$ is an economically feasible approach to treat painful bone metastases. Comparing to existing radiopharmaceutical agents intended for therapy of painful bone metastases, radiopharmaceutical agents that have been developed on the basis of generator-produced radionuclide Rhenium 188 (e.g. $^{188}$Re-HEDP, $^{188}$Re-zoledronic acid), allow to believe in the explicit economic advantage in future when implementing into clinical practice.

Keywords: Pharmacoeconomics, Zoledronic acid, Bone metastases, Radiopharmaceutical.

INTRODUCTION

According to the World Health Organization (WHO), cancer is one of the leading causes of death in the whole World - in 2012, an estimated 8.2 million (mln) people died from cancer. Each year, most cancer-induced deaths are caused by malignant neoplasms of the lungs, stomach, liver, colon and mammary gland. Over 60% of new cancer cases are registered in countries of Africa, Asia, Central and South America. 70% of all deaths are caused by cancer in these regions. According to the forecasts, cancer incidence will continue to rise from 14 mln in 2012 up to 22 mln in future decades [1].

In addition to irrecoverable losses of human lives, the high of cost oncological diseases contributes to the healthcare system not only in a direct financial term, but also in the form of indirect expenses, such as loss of production output due to the disability period (morbidity cost) and untimely death (mortality cost). Additional hidden cost can include transportation of patients, housekeeping cost and other supporting facilities [2]. Recent evidence suggest that comparing to other major causes of death, oncology diseases remains the most destructive impact on the world [3]. In a recent study by Harvard School of Public Health, researchers have counted that in 2010 the total financial cost of a 13.3 mln new registered cancer cases worldwide was around 290 billion (bln) United States Dollars (USD). The major part of the expenses (53%) consisted of a direct cost, while non-medical finances and costs associated with the disability-related time loss amounted around 67 bln USD and 69 USD bln respectively1. It is expected that by 2030 the total cost will grow up to 458 bln USD [4]. Along with that, according to the American Cancer Society and LIVESTRONG® estimates, excluding annual direct costs, oncology related economic losses will achieve up to 895 bln USD in the whole world [3]. It is remarkable that according to the social and economic study death is the most expensive process in the financial provision of the health care system, since financial costs by the end of the life amount to 12% of the whole medical provision budget, while 27% of the whole medical insurance budget1 is spent within the last 30 days of patient’s life [5].

Pharmacoeconomic (PhE) studies of radionuclide therapy for palliation of bone pain metastases are quite limited in the world. Moreover, most of the published PhE studies are performed using the "costs minimization" method, which is a very limited approach to the health care economics, as it is based only on cost comparison between different treatment methods. Some studies were carried out upon $^{89}$SrCl$_2$ in the 90s [6-8] making it impossible to adapt the data to present time due to the rapid changes of the therapy regimens, appearance of modern effective methods of pain syndrome control, and other external factors.

In a retrospective study researchers indicated a significant reduction of a total cost (by 5 696 $CAD) among patients with malignant neoplasm of prostate, who took $^{89}$SrCl$_2$. It has been suggested that financial

1 This context implies federal medical insurance program Medicare for the elderly population (over 65 years old) incorporated in the USA in 1965.
savings were associated with the reduction of a direct
cost of radiation therapy (RT), as well as the cost
associated with the services usage [6]. Furthermore, [7]
reported similar direct costs reduction among patients
with the metastatic hormone refractory prostate cancer
(MHRPC). Based on research evidence, inclusion of
\[^{89}\text{SrCl}_2\] to the regimen of metastatic bone therapy
allows to reduce costs for RT [7].

The financial aspect of pharmaceutical pain
management therapy for cancer patients can be quite
considerable. Clinical experience established that most
of the patients require significant doses escalation,
which is related to disease progression and leads to
addiction to analgesic agents. In another study
researches showed that application of \[^{89}\text{SrCl}_2\] or \[^{153}\text{Sm-}
EDTMP\] allows to reduce the total cost of pharmacological
pain-management therapy, thus reduce the total cost of the analgesic therapy [8].

Appropriate PhE analysis (for example, by “costs-
effectiveness”, “costs-utility” methods) seems to be
quite difficult to accomplish, due to multiple economic
variables related to the cost of Systemic Radionuclide
Therapy (SRT)(delivery, synthesis of radiopharmaceuti-
cal, administration, monitoring, etc.), costs of the side
effects therapy, organization and expenses saved
during the SRT process. Reasonable cost for SRT can
vary in different countries; for example, in the USA
radionuclide therapy of painful bone metastases is
estimated around 3 000-8 000 USD, in Korea – 2 400
USD, in China – 100 USD, in Europe – 1000 USD [9].

Other studies were performed in the 2000s,
providing results of the pharmacoeconomic analysis
carried out by “disease cost” [10] (2007), “costs-
effectiveness” (2005- [11], 2006 – [12])\(^1\) and “costs-
utility” (2012 - [13]) methods.

It might be interesting to focus on the “disease cost”
method carried out with SRT using \[^{153}\text{Sm-EDTMP}\] for
patients (N=712) with MHRPC, accompanied by the
pain syndrome. In this study, 85 patients (11,9%) were
given \[^{153}\text{Sm-EDTMP}\], 299 patients (42,1%) were given
RT, 167 patients (6,6%) were given pamidronic acid,
42 patients (6,6%) – Mitoxantrone and 119 (16,7%) –
opioids. The therapy was carried out till the optimal
cost over the pain syndrome was reached for all
patients. Additionally, all patients were followed-up for
12 months after the therapy has started. Results
showed no statistically significant difference between
all groups in social-demographic features or prostatic
specific antigen level (PSA). Opioid therapy appeared
to be the most expensive method for the in-patient
charge, comprising the largest portion of the expenses,
while RT was the most expensive method for the out-
patient charge. Importantly the least expensive method
both, in the in-patient and the out-patient charges, was
the SRT CPT\[^{153}\text{Sm-EDTMP}\]. Researchers recommend
to consider SRT as a low-cost, effective and safe
approach of pain syndrome management among
patients with MHRPC [10].

Important to draw the attention to another study of
the economic evaluation of \[^{153}\text{Sm-EDTMP}\] application
in Canada. Despite that \[^{153}\text{Sm-EDTMP}\] was registered
in Canada in 1997, clinical benefit of the drug has not
been funded in any province. According to this study,
the average cost of a conventional analgesic therapy
for one patient was around 26 075 Canadian Dollars
(CAD), while the total cost for all needing patients
(n=539) was 14 054 425 CAD. The average cost of the
analgesic therapy with \[^{153}\text{Sm-EDTMP}\] application for
one patient was equal to 11 680 CAD, and the total
costs for 539 patients was 6 295 520 CAD. By the
time the article was prepared, the net cost of \[^{153}\text{Sm-EDTMP}\]
was estimated of 4 500 CAD. With this price, the total
cost for all scheduled SRTs (755 SRTs)\(^1\) with
application of \[^{153}\text{Sm-EDTMP}\] in Canada will around 3
397 500 CAD. Thus, the investments of a 3 397 500
CAD into SRT by \[^{153}\text{Sm-EDTMP}\] for palliation therapy
for patients with painful bone metastases, will lead to
the economy of 7 758 905 CAD and realisation by the
return of investment (ROI) will be equal to 228% [13].

The cost effectiveness analysis of \[^{153}\text{Sm-EDTMP}\]
(Quadramet\(^6\)) application for pain management among
patients with prostate cancer and bone metastasis has
previously been carried out [11]. To perform the
analysis, researcher applied the “decision tree” model.
Patients, who could not achieve an absolute pain
control without conventional analgesic therapy were the
potential candidates to start treatment with \[^{153}\text{Sm-}
EDTMP\] or they could continue the conventional
therapy with dose escalation (time interval was 4
months). The potential adverse effect of pharmacological
therapy or necessity in the adjuvant
therapy was also considered. Effectiveness data
applied in the model was taken from the double blind
clinical trial (N=152) among patients with MHRPC,

\(^{1}\) Both studies are presented in the national languages, the first – in Spanish
and the second – in Portugese, which considerably limits availability of the
study results.
accompanied by the pain syndrome. The direct cost estimation was based on the cost of medical assistance\textsuperscript{3} according to SOIKOS (See Tables 1 and 2). Prices for medical drugs were taken from the medical catalogue. The cost was expressed in Euro as for 2004.

Present investigation displayed that from the costs-

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|}
\hline
\textbf{Visits to doctors} & \% & \textbf{Mean Value for 4 Months, Therapy Regimen} & \textbf{Cost, €} \\
\hline
Pain management specialists & 40 & 7 & 47.82 \\
Oncologist & 60 & 7 & 47.32 \\
General practitioner & 100 & 4 & 17.45 \\
\hline
\textbf{Procedures} & & & \\
Biochemical blood analysis, complete blood count & 100 & 1 & 10.38 \\
Biochemical blood analysis, complete blood count (AE) & 100 & 2 & 10.38 \\
Bone scanning & 100 & 1.5 & 163.68 \\
\hline
\textbf{Hospitalization} & & & \\
Hospitalization (AE) & 1.5 & 10 & 271.40 \\
Day patient department & 100 & 1 & 149.74 \\
\hline
\textbf{Medicines} & & & \\
\textsuperscript{153}\textsuperscript{Sm}-EDTMP & 100 & - & 466.01 \\
\hline
\textbf{NSAIDs (one of the following)} & & & \\
Ibuprofen & 100 & 600 mg/8 h/4 months & 53.60 \\
Diclofenac & 50 mg /8 h/4 months & 53.60 \\
Flurbiprofen & 50 mg/8 h/4 months & 53.60 \\
Fentanyl (stripes) & 15 & 600 µg /12 h/4 months & 418.13 \\
Dexamethasone & 12.5 & 2-3mg/8h/2 months & 5.68 \\
Amitriptyline & 12.5 & 25-75 mg /day/4 months & 1.73 \\
Gabapentin & 20 & 1.200-1.800 mg/day/ 4 months & 64.63 \\
\hline
\end{tabular}
\caption{Treatment Regimens Cost of Therapy by \textsuperscript{153}\textsuperscript{Sm}-EDTMP \textsuperscript{4} \cite{11}}
\end{table}

effectiveness point of view, the therapy by \textsuperscript{153}\textsuperscript{Sm}-EDTMP was a more reasonable and financially effective approach (see Table 3). Study findings and sensitivity analysis results indicated that the strategy with \textsuperscript{153}\textsuperscript{Sm}-EDTMP application was the dominant one, \textit{i.e.} it had the largest effectiveness and less cost for treatment than the conventional therapy\textsuperscript{5}.

However, it should be emphasized, that therapy regimens vary depending on the medical context, since pain is treated by different specialists and often is

\textsuperscript{3} Costs for medical assistance included radiation therapy, medication treatment and visits to the specialists, instrumental and laboratory examinations and in-patient stay.

\textsuperscript{4} According to the specialists, consideration of accurate regimens is complicated by the explicit differences between the patients. In the whole, dose of opioids administered simultaneously with\textsuperscript{153}\textsuperscript{Sm}-EDTMP was reduced by 20% in contrast to the conventional therapy, the exception was fentanyl therapy which remained unchanged.

\textsuperscript{5} Except for the theoretical cases hardly possible in practice, which suggest that application of biphosphonates is equal to 0%, and pain intensity reduction against background of \textsuperscript{153}\textsuperscript{Sm}-EDTMP continues for 2 months only. Increase of costs for on patient in such cases will amount to 630,04 € and 888,76 € respectively.
determined by the level of medical center infrastructure. Treatment cost calculation is often based on the level of agreement between different medical expertise and specialists. Thus a mean value was considered, which possibly does not correspond to the actual data in a certain medical center, but rather reflects the average state of a medical practice in Spain.

Table 2: Treatment Regimens in the Conventional Therapy\(^6\) [11]

<table>
<thead>
<tr>
<th></th>
<th>%</th>
<th>Mean Value for 4 Months, Therapy Regimen</th>
<th>Cost, €</th>
</tr>
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<tbody>
<tr>
<td>Visits to doctors</td>
<td></td>
<td></td>
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<tr>
<td>Pain management specialists</td>
<td>33</td>
<td>7</td>
<td>47.82</td>
</tr>
<tr>
<td>Pain management specialists (AE)</td>
<td>4</td>
<td>1.5</td>
<td>47.82</td>
</tr>
<tr>
<td>Urologist</td>
<td>63.75</td>
<td>1</td>
<td>52.34</td>
</tr>
<tr>
<td>Oncologist</td>
<td>95</td>
<td>6</td>
<td>47.32</td>
</tr>
<tr>
<td>Oncologist (AE)</td>
<td>6</td>
<td>1.5</td>
<td>47.32</td>
</tr>
<tr>
<td>General practitioner</td>
<td>100</td>
<td>4</td>
<td>17.45</td>
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<tr>
<th>Procedures</th>
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<tbody>
<tr>
<td>Biochemical blood analysis, complete blood count</td>
<td>95</td>
<td>1.5</td>
<td>10.38</td>
</tr>
<tr>
<td>Biochemical blood analysis, complete blood count (AE)</td>
<td>10</td>
<td>1</td>
<td>10.38</td>
</tr>
<tr>
<td>X-Ray study</td>
<td>25</td>
<td>1</td>
<td>16.56</td>
</tr>
<tr>
<td>X-Ray study (due to the adjuvant therapy)</td>
<td>15</td>
<td>1</td>
<td>16.56</td>
</tr>
<tr>
<td>X-Ray study of the abdominal cavity organs (AE)</td>
<td>1</td>
<td>1</td>
<td>163.6</td>
</tr>
<tr>
<td>Bone scan</td>
<td>100</td>
<td>1.5</td>
<td>163.6</td>
</tr>
<tr>
<td>Radiation therapy</td>
<td>70</td>
<td>4-10 сеансов</td>
<td>23.35</td>
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<table>
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<tr>
<th>Hospitalization</th>
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<tbody>
<tr>
<td>Hospitalization</td>
<td>5</td>
<td>15</td>
<td>271.4</td>
</tr>
<tr>
<td>Hospitalization (AE)</td>
<td>6.5</td>
<td>6</td>
<td>271.4</td>
</tr>
<tr>
<td>Day patient department</td>
<td>20</td>
<td>4</td>
<td>149.7</td>
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<tr>
<th>Medicines</th>
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<tr>
<td>Ibuprofen</td>
<td>100</td>
<td>600 mg/8h/4months</td>
<td>53.60</td>
</tr>
<tr>
<td>Diclofenac</td>
<td></td>
<td>50 mg/8h/4months</td>
<td></td>
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<tr>
<td>Flurbiprofen</td>
<td></td>
<td>50 mg/8h/4months</td>
<td></td>
</tr>
<tr>
<td>Metamizol</td>
<td>20</td>
<td>500 mg/6h/4months</td>
<td>11.18</td>
</tr>
<tr>
<td>Fentanyl (stripes)</td>
<td>15</td>
<td>600 µg/12h/4months</td>
<td>418.1</td>
</tr>
<tr>
<td>Fentanyl (patches)</td>
<td>32.5</td>
<td>100-200mg/3days/4months</td>
<td>67.29</td>
</tr>
<tr>
<td>Peroral morphine</td>
<td>50</td>
<td>120-400mg/day/4 months</td>
<td>170.3</td>
</tr>
<tr>
<td>Injection morphine</td>
<td>10</td>
<td>40-150mg/day/4 months</td>
<td>43.82</td>
</tr>
<tr>
<td>Morphine via individual catheter</td>
<td>3.5</td>
<td>8 mg/day epidurally</td>
<td>15.53</td>
</tr>
<tr>
<td>Methadone</td>
<td>10</td>
<td>20 mg/day/4 months</td>
<td>11.68</td>
</tr>
<tr>
<td>Lactulose</td>
<td>90</td>
<td>30 mg/day/4 months</td>
<td>59.19</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>1</td>
<td>60 mg/day/4 months</td>
<td>0.26</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>12.5</td>
<td>2-3mg/8h/2months</td>
<td>5.68</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>12.5</td>
<td>25-75mg/day/4 months</td>
<td>1.73</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>20</td>
<td>1200-1800mg/day/4 months</td>
<td>64.63</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>20</td>
<td>4 mg/4weeks/4months</td>
<td>252.4</td>
</tr>
</tbody>
</table>

\(^6\) It shall be noted that therapy duration was 4 months not for all patients (which is determined by opioids rotation); it is demonstrated in the table in the form of percent from the total patient's number, who were given therapy, on condition that all the patients were given any type of opioids within the described time period.

In respect to the final results of the study, the main conclusion implies that \(^{153}\)Sm-EDTMP is a cost-effective and efficient method of pain management for patients with MHRPC and bone metastases. Moreover, it shall be specified that \(^{153}\)Sm-EDTMP is highly effective for all patients with metastatic pains, regardless of their origin, in case when such metastases are discovered during a routine bone scanning.

Therefore, in recent 20 years only 7 studies were published on pharmaco-economic study of the skeleton's radionuclide therapy, despite a wide spread application of this technology in clinical practice in the whole world.

It should be noted that a new radiopharmaceutical \(^{228}\)Ra is designed for castration-resistant prostate cancer with symptomatic bone but without visceral metastases, has a different to \(^{153}\)Sm, \(^{188}\)Re and \(^{186}\)Re clinical indications. Despite of that there is The National Centre for Pharmacoeconomics (NCPE) publication related to the \(^{228}\)Ra that presents the cost-effective analysis of \(^{228}\)Ra vs. best supportive therapy (based on the overall trial population data), \(^{228}\)Ra versus abiraterone (based on post-docetaxel population trial data but following NCPE assessment of the company.
submission, the NCPE considers that the cost effectiveness of $^{228}$Ra has not been demonstrated [14]. In 2016 The Global Journal of Health Science documented several studies reporting data on the use of radium-223 (which is an alpha-emitting radioisotope that targets areas of osteoblastic metastasis and is Food and Drug Administration (FDA) approved) for treating mCRPC from the point of pharmacoeconomics review [15] by NCPE [14], The Ludwig Boltzmann Institute, NICE, German Institute for Quality and Efficiency in Health Care (IQWiG), Aberdeen HTA group (National Institute of Health Research (NIHR) and Swedish National Board for Health and Welfare. As authors mentioned in the review “studies reporting any figures on the cost-effectiveness of this therapy were generally of a low quality. Most guidelines did not include any economic considerations when giving their state of art. When cost was mentioned, the guidelines gently touched the item by mentioning there are costs” [15]. Consequently, $^{223}$Ra-therapy is a not cost-effective approach and there is an insufficient data for final conclusions. Thus, there is a very limited support for health care administrators because of it’s price.

Recently researchers have been interested in $^{177}$Lu-labeled ethylenediamine tetramethylene phosphonic acid ($^{177}$Lu-EDTMP), which is an agent that concentrates in areas of enhanced osteoblastic activity. Some studies show that $^{177}$Lu-EDTMP could be used as an effective therapeutic radionuclide for palliation of metastatic bone pain [16]. Moreover, Lutetium-177 has favourable characteristics, such as low energy $\beta^-$ emission, which should reduce the toxicity. Preliminary studies have already confirmed selective tracer accumulation in the skeletal lesions [16]. However, the number of clinical trials is very limited. Moreover, most of the studies are underpowered due to the insufficient number of participants, as well as lack of a randomization and alternative treatment arm. Moreover, there are no evidence of the financial advantages of $^{177}$Lu-EDTMP over other agents. Thus, it is impossible to conduct a cost-effective analysis. The work is still ongoing and further investigation of the $^{177}$Lu-EDTMP effectiveness for the palliation therapy of metastatic bone pain and it’s financial cost during the therapeutic course is required as well as it's financial implication in treatment strategy.

Currently there is a rapid development of other radiopharmaceutical agents that apply generator-produced isotope, such as $^{188}$Re-zoledronic acid and are designed for the skeleton’s metastatic lesions therapy. It should be expected, that due to the availability of $^{188}$Re generators, as well as the convenience of $^{188}$Re receipt directly in the ward, there will be a reduction of the net cost of radiopharmaceutical agent’s production along with the increase of therapeutic performance and reduction of side effects. However, the data about the cost of radiopharmaceutical agent’s production on the basis of $^{188}$Re is limited. Therefore, in order to conduct a comprehensive evaluation of the technologies based on $^{188}$Re, valid pharmacoeconomic studies should be conducted in nearest future.

### Table 3: Results of the Pharmacoeconomic Effectiveness Analysis

<table>
<thead>
<tr>
<th></th>
<th>Conventional Therapy, €</th>
<th>Therapy by $^{153}$Sm-EDTMP, €</th>
<th>Incremental “Cost-Effectiveness” Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct costs</td>
<td>2 252.77</td>
<td>2 126.30</td>
<td>$^{153}$Sm-EDTMP – dominant</td>
</tr>
<tr>
<td>Complete response</td>
<td>18</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Costs for the patient</td>
<td>12 515.39</td>
<td>5 595.52</td>
<td></td>
</tr>
</tbody>
</table>

CONCLUSION

Today, the field of radionuclide diagnostic and therapy is going through an extremely interesting phase. Recent significant technological advances make it very likely that radiopharmaceuticals will become an important part of diagnostic and therapy of various forms of cancer. Despite that the potential of radionuclides in treatment has been recognised a while ago, the area is strongly underinvestigated. Most of studies are performed locally with small amount of participants, which makes them statistically underpowered. As a results it is impossible to perform a valid pharmacoeconomic evaluation and analysis, which in fact prevents application of a nuclear medicine’s methods to clinical practice. Thus, in order to continue research and create an optimal therapeutic and financial strategy for patients, industry calls for further investments.
REFERENCES


