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Cost minimisation analysis – a simple concept, yet difficult to implement. Too simple CMA can lead to unauthorized conclusions

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Abstract

Background: AOTMiT's Health Technology Assessment guidelines developed in Poland in 2007 along with their subsequent updates do not specify how a cost minimisation analysis should be carried out. Hence, there is a lot of latitude in terms of the manner in which it is developed. Authors of specific cost minimisation analyses should adjust the methodology of their analysis to ensure that its utility for the decision-maker is as high as possible, and the best solution is selecting such a methodology which reflects the clinical reality best. In line with the NICE methodology, a cost minimisation analysis can be carried out only when there is strong evidence supporting lack of differences between the compared health interventions.

Methods: The objective of this article is to present a critical assessment of the methodology of two CMAs on the example of selected economic analyses published on the AOTMiT website (along with verification analyses) together with proposal of their improvement.[7, 9] They were chosen due to the specificity of the health intervention they compare. The selected analyses compare health interventions differing in: the treatment regimens, route of administration and duration of use. The identified limitations of the analyses regarded the length of the time horizon adopted in the analysis, the cost calculation method or assessment of the justification of comparator selection.

Results: The CMA for cladribine tablets is characterised by limitations associated both with the length of the time horizon and the cost calculation method.

In the case of the cost minimisation analysis for cabazitaxel, the identified limitations are: taking into account the same treatment duration for the compared health interventions (an approach suggested in the AOTMiT's verification analysis)[9] and the use of treatment duration medians in calculations, which resulted in a one-year time horizon being adopted.

In connection with the limitations identified in both analyses, the authors hereof have decided to adopt an approach which is the close to the actual situation on the example of cabazitaxel, in which the simplified modelling allows for reducing the impact of limitations identified in both CMAs (and the cabazitaxel verification analysis), related to the time horizon duration of the analysis, the calculation method, the use of medians and the right comparator selection. The statutory ex-factory price of cabazitaxel determined in the new analytical approach is nearly three-times higher (an increase by 169%) than the threshold price calculated by the AOTMiT.

Conclusions: A simple cost minimisation in which the maximal cost of therapy incurred in a given time should be reserved solely for situation where obvious lack of differences has been demonstrated. In the case of developing a cost minimisation analysis for more complex cases, the analysis should be based on modelling of both effects and costs in a similar manner as a typical cost effectiveness/cost utility analysis.

Introduction

One of the objectives of Health Technology Assessment (HTA) is determining the cost-effectiveness of the assessed health intervention in an economic analysis. Cost-effectiveness is determined on the basis of analyses which compare the assessed heath intervention with its comparators in terms of costs and health results.[1] The basic types of economic analyses used in HTA include:

- CUA: Cost-Utility Analysis
- CEA: Cost Effectiveness Analysis
- CBA: Cost Benefit Analysis
- CCA: Cost Consequence Analysis
- CMA: Cost Minimisation Analysis

The first three types of economic analyses are used when the compared interventions differ in terms of effectiveness and safety. A cost consequence analysis is used most often when it is not possible to make a comparison between the health interventions based on existing evidence. Such an analysis results in a comparison of costs and health effects. A cost minimisation analysis is a specific type of cost-effectiveness analysis which is conducted when the compared health interventions are characterised by equal effectiveness (both efficiency and safety).[1]

Cost minimisation analysis has been described in the AOTMiT guidelines in the following manner.

Authors of the AOTMiT guidelines do not specify how a cost minimisation analysis should be performed, leaving much freedom as to how it should be carried out. Authors of specific cost minimisation analyses should adjust the methodology of their analysis to ensure that its utility for the decision-maker is as high as possible and reflects the clinical reality best. In many cases, cost minimisation analysis is chosen from among the various types of economic analysis because it can be easily understood by the decision-maker due to its simple and clear form. A minimisation analysis must be developed in a methodically correct manner so that its results are not misinterpreted. Under Polish conditions, in the reimbursement process, the impact of the economic analysis on negotiations is important due to the calculation of the threshold price and in many cases the adoption of a simplified approach to CMA leads to its amount being distorted.

The cost minimisation analysis was widely described in literature, among others in M. Drummond's book - one of the HTA fundamental books in the opinion of the authors.[17] The discussion on the methodology to be adopted in cost minimisation analyses is still under way, and its summary is presented in the article by A. Briggs published under the significant title "The death of cost-minimization analysis".[2] Authors of this paper wish to state that a cost minimisation analysis can only be carried out if there is strong scientific evidence that there are no differences between the compared health interventions. Also in the opinion of NICE, the cost minimisation analysis should be reserved only for exceptional situations (obvious cases – that is, where there are no doubts as to the differences in performance parameters between the compared health interventions); in other cases, performing another type of analysis is recommended (in such cases it usually is a cost-effectiveness analysis or a cost-utility analysis).[5, 6] All these publications indicate that in more complex or unusual situations, the methodology of cost minimisation analysis should refer to the methodology used in the cost-effectiveness or cost-utility analyses, where the economic model is the basic tool. Unlike cost-effectiveness or cost-utility analyses, in CMAs, the result is the cost difference between the compared therapeutic options and the health outcomes will be disregarded.

In simple cases – for example, the comparison of two orally administered hypertension drugs (as "me too drugs") used daily – it is enough to prepare a simple analysis of minimising costs in an annual time horizon. Calculations are often carried out as multiplying the length of the time horizon expressed in days by the daily therapy cost. More complicated cases – e.g. a comparison of an intervention used once with a drug administered in cycles – require preparation of a more complex analysis, in which modelling using multiple variables will be used. This means that a full or simplified economic model should be created, which forces the development of an accurate and correct methodology and a much greater number of calculations. Elaboration of a cost minimisation analysis which is correct, i.e. in line with best practices, should promote transparency in the process of the reimbursement application assessment by the AOTMiT and at further stages of the reimbursement process.

The objective of this article is to present two recent examples of analyses in which a cost minimisation analysis was carried out, when different routes of administration are used and the potential for different treatment schedules is different. Both analyses, published on the AOTMiT website[7, 8, 9, 16] (along with verification analyses), were subject to a critical evaluation of the CMA methodology. In the article we would like to propose a methodical approach which would help avoid the limitations identified in the methodology evaluation based on one of the selected cases of CMA analysis.

Methods

The analysed elements of the CMA methodology

Time horizon in the cost minimisation analysis

The HTA guidelines indicate that the time horizon of economic analysis should be long enough to allow for assessing the differences between the results and costs of the compared health interventions, while in the case of a cost minimisation analysis, a unit length of the time horizon can be assumed (month, year, etc.) only when the costs related to the use of the compared health technologies are constant over time.[1] At this point it should be noted that equal effectiveness of drugs does not always

Table 1. Cost minimisation analysis in the AOTMiT guidelines dated 2016[1]

Chapter	Content of the guidelines
4.3 Time horizon	In the case when the economic analysis focuses on cost minimisation and the costs associated with the use of compared health technologies are constant in time, a unit length of the time horizon may be assumed, e.g. 1 year.
4.4. Analytical method	If clinical equivalence of the compared health technologies has been established as part of the clinical analysis or if the differences between them are not clinically relevant, a cost minimisation analysis should be performed.
4.4.3. Cost minimisation analysis	A cost minimisation analysis is presented if the existing evidence confirms that the health outcomes (effectiveness of compared health technologies) are therapeutically equivalent. In such a case, the analysis consists only in a cost comparison.

go hand-in-hand with an identical treatment regimen for patients. For example, the assessed intervention is applied daily until the disease progresses, and its comparator is used only once and disease progression appears at the same time for both drugs. Equal effectiveness of therapies determines the type of economic analysis (assuming there are no differences in safety), while the time horizon of the analysis should equal at least the time until progression of the disease occurs. Adoption of such an approach, with regard to the time horizon of the analysis, will allow taking into account both the equal effectiveness of the compared interventions, as well as the costs taking into account the specificity of treatment methods with both interventions.

The method of calculating costs – the therapy duration

The methodology of the cost minimisation analysis assumes that all compared therapies are equal in terms of effectiveness, and this effectiveness has been proven under specific conditions, in particular during the treatment periods in accordance with the protocol of relevant clinical trials. This means that modifying therapy duration in the CMA analysis, as compared to durations reported in clinical trials, assumes that the drugs have higher/lower effectiveness than the efficacy reported in these trials. The adoption of the same therapy duration, and thus – also the selected time horizon (e.g. 1 year) – is possible only for drugs with a similar dosage/application regimen. In other cases, modifying the length of therapy should be approached with caution and other solutions are suggested.

The following approaches can be used to determine the treatment duration:

- all patients use the given health intervention throughout the entire time horizon of the analysis – that way the maximum cost associated with the use of a given health intervention is calculated.
- not all patients use the given health intervention throughout the entire period covered by the cost minimisation analysis – some of them lose their response to treatment, die, experience adverse effects which require discontinuation of treatment. If this element is included in the analysis, then the cost calculated that way will be the probable average cost associated with the use of the given health intervention. To take this parameter into account, the following data acquired in the course of clinical trials can be used:
    - TTD (time to treatment discontinuation),
    - DOT (days of therapy),
    - mean or median treatment duration,
    - the mean or median amount of active substance consumed by the patient,
    - the percentage of patients continuing therapy,
    - patient-years,
    - presented costs of therapy

Performing calculations taking into account median treatment duration, instead of the mean, may not reflect the objective of the economic analysis, i.e. estimation of the mean cost (rather than the median of costs), which allows to determine the average incremental value. If the cost of the analysed health intervention is estimated on the basis of the median of the treatment duration, then the obtained result should be understood as the median of the cost of therapy (not the average cost of therapy). If the other cost categories in the economic analysis were determined as mean values (estimated as mean unit costs multiplied by the incidence rate of individual events in the clinical trial), then the median sum for the cost of therapy and mean for other cost categories to determine the total costs in the intervention arm, and then the calculation of incremental costs yield irrelevant results.

It should also be noted that the following statement is also included in the AOTMiT guidelines: *The results of the economic analysis should be presented in the form of total health results taken into account in the economic analysis and separately the total costs of the compared technologies, individual cost categories, the difference in total costs and health outcomes, the difference in individual cost categories. The results should be presented in the form of the mean value along with measures of dispersion (derived from the probabilistic analysis).*[1]

Similarly, in the NICE guidelines[7], it was clearly indicated that it is correct to estimate the time to occurrence of an event based on averages:

- *(…) health economic models are built to characterise the decision problem and uncertainty – and mean estimates are required to address the decision problem.*
- *Mean time-to-event should be estimated rather than medians.*

For example, in the case of the left-side treatment duration distribution, adopting the median therapy time – instead of the mean – leads to a significant unjustified over-valuation of the drug cost. The median treatment duration, unlike the mean, may also not include a limitation on the maximum treatment duration, in line with the SmPC or the content of the drug programme (cutting off data does not affect the median value if it is lower than the maximum limit).

Results

Selection of analyses

Two economic analyses assessed by the AOTMiT in 2018 and 2019 were analysed, along with the verification analyses prepared by the AOTMiT.[7, 9] They were chosen because of the specificity of the health interventions they compared. Both cabazitaxel used in the treatment of prostate cancer and cladribine tablets used to treat multiple sclerosis, have different dosing/use regimens than their comparators used in the economic analysis. Therefore, the decision was made to look into the methodology of each of these analyses in terms of compliance with the methodology of conducting cost minimisation analyses, described in the AOTMiT guidelines, as well as the utility of the analyses for the decision-maker. The HTA report for cladribine tablets was assessed by the AOTMiT in 2018 and received a positive recommendation from the President of this agency, when the article was prepared the HTA report for cabazitaxel was evaluated by the AOTMiT.

The second drug presents a more accurate analytical approach which will take into account: differences in dosages between comparators, use of mean values instead of the median, rejection of the assumption of an equal treatment duration for the compared health interventions and elimination of one of the comparators.

The main limitations identified in these two analyses relate to two areas: the time horizon of the analysis and the method of calculating costs over time. The selection of the right comparator, which will be replaced if the assessed intervention indeed receives coverage, constitutes an additional limitation.

Findings in the analysed economic parts of the HTA dossiers

Economic analysis for cladribine[8]

The first example was the HTA report published on the AOTMiT website, comparing cladribine tablets (MAVENCLAD) with alemtuzumab, natalizumab and fingolimod in the treatment of relapsing-remitting multiple sclerosis with high disease activity. The methodology of the published economic analysis was as follows:

1. Disease: Multiple Sclerosis
2. Comparators: alemtuzumab, natalizumab, fingolimod
3. Type of analysis: cost minimisation analysis for selected comparison pairs,
4. The basis for adopting the analysis methodology: indirect comparison carried out as part of the clinical analysis.
5. Perspective: an entity required to finance services from public funds (NFZ).
6. The calculation method: product of unit costs and treatment duration.
7. Time horizon: 5 years
8. Discounting: 5% for costs per year
9. Costs included in the analysis: the compared substances, administration or distribution of drugs, premedication accompanying the drugs, treatment of adverse reactions, monitoring under the drug programme, monitoring after completion of active treatment under the drug programme, and costs of subsequent therapy after treatment with cladribine tablets is completed.
10. Treatment duration: presented in the table below.

A five-year time horizon was adopted in the analysis. The maximum treatment duration for alemtuzumab does not exceed 5 years. At the time of preparing the economic analysis, the treatment duration for natalizumab was limited to 5 years. Only fingolimod therapy could last longer. Treatment with cladribine tablets is carried out in two short cycles, administered at the beginning of two consecutive years. After the end of the 2 treatment cycles, no further treatment with cladribine is required in year 3 and 4. The analysis assumes that the duration of treatment with cladribine tablets does not exceed 2 years, with an additional 2 year-period without active treatment, but with the clinical effect maintained.[7]

Due to the fact that the time of using most comparators may be up to 5 years under drug programmes, an analogical length of the time horizon was assumed for the economic analysis. The 5-year time horizon allows for taking into account the possible maximum duration of treatment with alemtuzumab and natalizumab within drug programmes, and thus the full effect of treatment with these comparators.[7] The authors of the analysis,

Table 2. Duration of individual drug therapy in the CMA for cladribine

Drug	Maximum treatment duration	Treatment duration in the analysis		Data source
Cladribine tablets	2 years*	2 years	100% of patients treated for two years	Economic analysis for cladribine tablets
Alemtuzumab	2 years*	2 years	100% of patients treated for two years	
Natalizumab	Until loss of effectiveness	5 years	100% of patients treated for five years	
Fingolimod	Until loss of effectiveness	5 years	100% of patients treated for five years	

** a small fraction of patients may receive further doses*

referring to the AOTMiT's remarks, indicate that adoption of a one-year time horizon would not be appropriate due to the special way in which alemtuzumab is administered, where the effect lasts longer than the period of active treatment. Therefore, a 5-year time horizon was considered to be the most appropriate for the analysis.
Failure to consider the probability of treatment discontinuation is a limitation of this cost minimisation analysis. This means that the cost of individual therapies calculated in the analysis is not the actual cost (taking into account the mean costs), and instead the maximum cost (calculated on the assumption that each patient is treated within the assumed time horizon appropriate for the given dose regimen). Authors of the analysis argue that it is necessary to model the costs after treatment discontinuation, which would entail arbitrary assumptions. Another argument used consists in the clinical analysis results, demonstrating that the probability of discontinuation of treatment in clinical trials was similar between the interventions.

In the economic analysis for alemtuzumab, published on the AOTMiT website, at the end of the fifth year, fingolimod therapy was continued by 41% of patients, and natalizumab – by 48% of patients. Based on these data, it can be assumed that adopting a 5-year time horizon in a cost minimisation analysis is appropriate for the comparison of cladribine tablets with alemtuzumab. In the case of the natalizumab and fingolimod comparison, the time horizon should be much longer, as the differences resulting from the different regimen of administering cladribine tablets as well as natalizumab and fingolimod have not been taken into account.

In the verification analysis[16], AOTMiT analysts considered it justified to perform a CMA with a shorter horizon (equal to 4 years) due to the period of treatment with cladribine consistent with the SmPC (2 years of drug administration and 2 years of observation). However, it is difficult to accept such an approach because it involves adjusting the horizon to the therapy with the shortest duration, which in turn causes the omission of significant costs incurred on comparators for which the treatment duration is longer. From the point of view of the AOTMiT guidelines[1], which recommend that the time horizon be "long enough to allow for the assessment of differences between the results and costs of the assessed health technology and its comparators", it seems that both the adoption of the 5-year horizon – as in the submitted analysis – as well as the 4-year horizon – as postulated in the verification analysis – is in the opinion of this publication authors inappropriate.[12, 16] The length of the time horizon in this analysis should be at least 10 or 15 years (when, in a simulation, a small percentage of patients continue the therapy) or the entire lifetime.

Economic analysis for cabazitaxel[7, 10]

As a second example of a CMA, the HTA report for the comparison of cabazitaxel (brand name Jevtana) with abiraterone acetate, enzalutamide or radium 223 dichloride was used to treat metastatic castration-resistant prostate cancer, and a verification analysis developed by AOTMiT were used. The methodology of the published economic analysis was as follows:

1. Disease: metastatic castration-resistant prostate cancer
2. Comparators: abiraterone acetate, enzalutamide, radium 223 dichloride
3. Type of analysis: cost minimisation analysis
4. Basis for adopting the analysis methodology: a comparison of evidence collected in the clinical analysis (naive comparison)
5. Perspective: an entity obliged to finance public benefits (NFZ) and NFZ + benefit recipient (patient)
6. The calculation method: the product of the treatment duration and unit costs of individual drugs
7. Time horizon: 1 year
8. Discounting: none
9. Costs included in the analysis: the compared substances, administration of drugs, combination of prednisone/prednisolone, G-CSF prophylaxis, drug programme qualification, monitoring under the drug programme, as well as costs incurred after treatment under the drug programme
10. Treatment duration: presented in the Table 3.

A one-year time horizon was adopted in the CMA. The authors of the analysis have made the assumption that all patients survive a year (the assumption is based on median total survival from clinical trials for individual health interventions).

Only parameters available in the trials, determining the treatment duration, were used to calculate the treatment cost. Cabazitaxel and radium 223 dichloride are administered in cycles of 21 and 28 days, respectively, while abiraterone acetate and enzalutamide are administered daily. To determine the treatment duration with cabazitaxel and radium 223 dichloride, medians of the number of therapy cycles were used, and for abiraterone acetate and enzalutamide, median treatment duration was used. The calculations were made by multiplying the unit costs by the appropriate treatment duration; furthermore the other costs and costs incurred after completing treatment under the drug programme were taken into account.

The CMA published on the AOTMiT website was based on data from another order of the Minister of Health made to the AOTMiT, in which the median length of therapy for enzalutamide and abirateron was used.[3] These data were used to calculate the treatment cost in the cabazitaxel cost minimisation analysis. The optimal method of calculating and presenting cost data is to use average values, which, however, have not been published, and the calculation of these values requires certain assumptions. In the case of a change in the data on treatment duration from medians to means, the one-year time horizon of the analysis can therefore be too short. The maximum duration of treatment with cabazitaxel and radium 223 dichloride is limited and amounts to 10 and 6 cycles, respectively, which means that for these two interventions, a one-year time horizon of the analysis is adequate, as no patient will be treated for more than a year. The maximum duration of treatment with abiraterone acetate and enzalutamide is not specified, and the median adopted for the calculations means that for half of the patients it is actually shorter and for the other half it is longer than the median. And therefore in fact some patients can be treated for more than one year, which leads to the conclusion that a one-year time horizon may be too short to compare those two drugs.

An even greater simplification of the analysis was proposed as part of the AOTMiT verification analysis. In the AOTMiT's opinion, the CMA the arbitrary assumption on the comparable effectiveness of cabazitaxel and its comparators made by the authors of the analysis means that comparing the costs of individual therapies incurred in different periods is not reliable.[9] The proposed approach, consisting in adopting the same treatment duration for all interventions (168 days as a common denominator for cabazitaxel and radium 223 dichloride), disregards the differences in the type of therapy (chemotherapy, hormonotherapy), in particular those related to treatment discontinuation due to the occurrence of adverse events and determining the maximum treatment duration for some interventions. As already mentioned, the methodology of a cost minimisation analysis assumes the same effectiveness of all compared treatment methods, however, it is achieved within the treatment duration strictly defined in the clinical trial protocol. Modifying treatment duration in relation to those reported in clinical trials is tantamount to assuming that the drugs have a higher/lower effectiveness than the efficacy indicated in clinical trials. However, in the approach proposed by the AOTMiT, the cabazitaxel treatment duration was significantly extended (8 cycles instead of 6 cycles, which means that the effectiveness of cabazitaxel therapy in this period is probably higher than reported in the TROPIC study)[10] and the enzalutamide treatment duration was shortened (168 days instead of 253 days, which means that the effectiveness of enzalutamide therapy in that period is probably lower than reported in the AFFIRM study)[3].

Following this line of reasoning, illustrated with the attempts of approaching the subject, it seems reasonable to propose and conduct an analysis based on the data on the treatment duration in clinical trials, i.e. in line with the methodology adopted in the submitted economic analysis. The adopted approach is free from the limitations described above (it takes into account the impact of AEs on the treatment duration and limitation of the maximum duration of treatment with cabazitaxel and radium 223 dichloride).

An additional limitation of the analysis for cabazitaxel is the selection of comparators and the associated method for determining the threshold price. In accordance with the MoH's Regulation on minimum requirements, in the case of CMAs (more broadly: when the circumstances of Article 13 (3) of the Reimbursement Act[12] are met), the threshold price should be set relatively to the comparator with the lowest cost utility ratio (CUR). In the case of the submitted analysis, that comparator was radium 223 dichloride. However, current clinical practice guidelines state that radium 223 dichloride can only be used in a small population of patients with symptomatic bone metastases without visceral metastases. In addition, the European Medicines Agency has issued a recommendation (EMA / 500948/2018[13]), which indicates that due to the increased number of fractures reported during clinical trials, the use of radium 223 dichloride should be limited to patients in whom two treatment lines were previously used, or for whom no other therapeutic options are available. Limitation of use have been included in the latest SmPC for radium 223 dichloride[14] and in the B.56 drug programme which has been in force since 1 January 2019.[15]

Table 3. Duration of individual drug therapy in the CMA for cabazitaxel

Drug	Maximum treatment duration	Treatment duration in the analysis		Data source
cabazitaxel	10 21-day cycles	6 21-day cycles (126 days)	Median number of cycles from the clinical trial	TROPIC[10]
abiraterone acetate	Until loss of effectiveness	5.6 months (=170 days)	Median progression-free survival	AFFIRM and HTA report[3]
enzalutamide	Until loss of effectiveness	8.3 months (=253 days)	Median progression-free survival	OU-AA-301 and HTA report[3]
radium 223 dichloride	6 28-day cycles	6 28-day cycles (168 days)	Median number of cycles from the clinical trial	ALSYMPCA[11]

Due to the above limitations of use of radium 223 dichloride, cabazitaxel will constitute a viable clinical alternative to hormonotherapy, while to a small extent it will replace treatment with radium 223 dichloride. According to NFZ data, in 2018, abiraterone acetate and enzalutamide were administered to 1494 and 552 patients, respectively (the data are incomplete – until October 2018). The number of patients treated with radium 223 dichloride was significantly lower in this period and amounted to 129 people.

Taking into account the number of the above-mentioned arguments, it should be noted that radium 223 dichloride should not be used as a comparator in the cost minimisation analysis, which will also translate into the threshold price.

Table 4. Comparison of differences in assumptions in the submitted analysis for cabazitaxel vs. the verification analysis

Parameter / assumption	The submitted CMA	Verification analysis
Treatment duration – data source	Determined on the basis of medians reported in clinical trials	Determined at the same level for all interventions – based on the median for radium 223 dichloride
Treatment duration – taking equal effectiveness into account	YES? – due to the heterogeneity of the trials, there is no possibility of an indirect comparison	YES
Treatment duration – taking treatment discontinuation due to AEs into account	YES	NO
Treatment duration – taking the impact of maximal treatment duration into account	YES	NO – assumptions were made for abiraterone acetate and enzalutamide, as if there was a maximum treatment duration limit
Comparator selection – inclusion of radium 223 dichloride	YES	YES

In summary, the main limitations of the analyses described above include:

- For the cladribine analysis:
  - An insufficiently long time horizon
  - Treatment discontinuation not taken into account
- For the cabazitaxel analysis:
  - The cost calculation method
  - An insufficiently long time horizon
  - Comparison made with the wrong comparator and thus calculation of the threshold price relative to radium 223 dichloride

In connection with the limitations identified in both analyses, the authors hereof have decided to adopt an approach which is the closest to the actual situation on the example of cabazitaxel, in which the simplified modelling allows for reducing the impact of limitations identified in both CMAs (and the cabazitaxel verification analysis), related to the time horizon duration of the analysis, the calculation method, the use of medians and the right comparator selection. In the case of the cladribine analysis, no proposal of the most accurate analytical approach has been presented, as it mainly consists in extending the time horizon and does not require a more detailed description.

CMA improved framework

CMA for cabazitaxel – a methodology proposal for conducting a CMA for different treatment durations using the compared health interventions

Taking into consideration the two identified limitations of the CMA for cabazitaxel submitted to the AOTMiT[7] and in the verification analysis prepared by the AOTMiT[9], we present our approach taking into account mean treatment duration instead of medians and rigid – arbitrally fixed – common treatment durations for all drugs, eliminating the inappropriate comparator and limitations related to the heterogeneity of clinical trials for the compared interventions. The approach proposed in the AOTMiT verification analysis[9], equalising the treatment durations, was presented in the assumption that there are no differences in the effectiveness of the compared interventions adopted in the economic analysis. However, it should be noted that the treatment duration is determined not only by effectiveness, but also by other factors (as described above). This means that any harmonisation of treatment durations should be adjusted to take into account the differences in the frequency of AEs and the maximum treatment duration.

In clinical trials for the compared interventions, the average treatment duration was not reported. This is a common situation due to the fact that – at the time when the study results are published – usually some patients continue the therapy and consequently it is impossible to determine the average treatment duration, in particular extrapolating the percentage of patients continuing therapy for a longer period than the clinical trial follow-up period.

In order to determine the average time of therapy in the proposed approach, the methodology based on the adjustment of the time to treatment discontinuation (TTD) curves for individual interventions was applied on the basis of the median treatment duration reported in the study. The median treatment duration is the only parameter reported for TTD, therefore there is no possibility to perform the match in a different way, in particular there are no Kaplan-Meier curves for TTD in the publications. In addition, almost all of the distributions most commonly used in the survival analysis require the determination of at least two distribution parameters (Weibull, gamma,

log-normal, log-logistic, Gompertz), the only exception is the exponential distribution parameterised using a single factor – the scale parameter . The median for the exponential distribution is defined as ln(2)/λ. In view of the above, modelling of the therapy time was carried out on the basis of exponential curves, which consequently means adopting a constant probability of interrupting the therapy over time.

In order to reduce the uncertainty regarding the heterogeneity of studies and the inability to compare the data reported in them, in particular regarding the treatment duration, three key assumptions were made:

- Assumption I: according to the adopted methodology (cost minimisation analysis), it was assumed that the compared interventions do not differ in terms of time to progression and – as a result – the treatment duration resulting from disease progression is the same for all therapies.
- Assumption II: it was assumed that differences in the frequency of adverse events (AEs) translate into differences in the treatment duration.
- Assumption III: it was assumed that determining the maximum treatment duration for cabazitaxel (CAB) affects the average treatment duration.

Based on the above assumptions, the process of determining the average treatment duration for individual interventions was carried out. The next steps of the performed calculations are presented below.

1. The exponential curve was adjusted to the median duration of cabazitaxel treatment presented in the TROPIC study.[10] That way, constant weekly probability of discontinuation of cabazitaxel therapy was determined — it amounts to 4.2%. This percentage takes discontinuation of therapy for any reason into account. The TTD curve for cabazitaxel (disregarding the maximum treatment duration limitation) is shown on Chart 1.

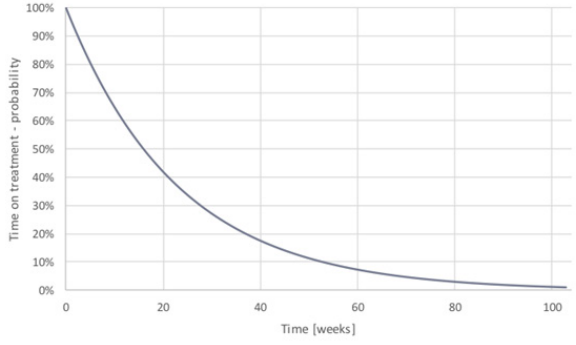

Chart 1. TTD curve for cabazitaxel (CAB)

2. The treatment duration curve has been corrected by "subtracting" treatment discontinuation due to the occurrence of AEs (assumption II was taken into account). In the TROPIC[10] study for cabazitaxel, the percentage of treatment discontinuation due to AEs was 18%, which translates into an average weekly probability of discontinuation of cabazitaxel therapy due to AEs equal to 0.7%. In consequence of that, the weekly probability of discontinuing cabazitaxel therapy for reasons other than occurrence of AEs (associated with disease progression – PFS) was set at 3.5% (interest difference of 4.2% and 0.7%). A comparison of the TTD and PFS curves for cabazitaxel is shown on Chart 2.

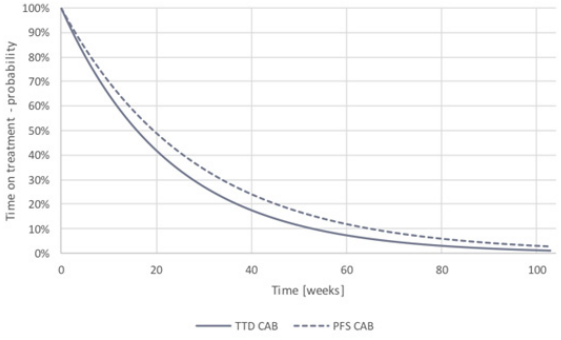

Chart 2. Comparison of the TTD and PFS curves for cabazitaxel

3. In line with assumption I it was assumed that the PFS curves for all compared interventions are the same, which means that the constant weekly probability of discontinuing treatment for reasons other than the occurrence of AEs is 3.5%.
4. The results of COU-AA-301[3] and AFFIRM[3] studies regarding the percentage of treatment discontinuation due to AEs were taken into account (again including assumption II):
a. for abiraterone acetate (ABI), the percentage was 19%, which translates into an average weekly probability of treatment discontinuation equal to 0.4%,
b. for enzalutamide (ENZ), the percentage was 8%, which translates into an average weekly probability of treatment discontinuation equal to 0.2%,
5. The weekly probability of treatment discontinuation for reasons other than AEs (3.5%) was compiled with the probability of treatment discontinuation caused by AEs and the total weekly probability of treatment discontinuation for comparators was determined. The obtained probabilities were as follows: 3.9% for abiraterone acetate and 3.7% for enzalutamide.
6. Assumption III was taken into account, i.e. the effect of the maximum treatment duration for cabazitaxel (30 weeks) on the actual treatment duration. On Chart 3, the final TTD curves for the compared interventions are summarised.

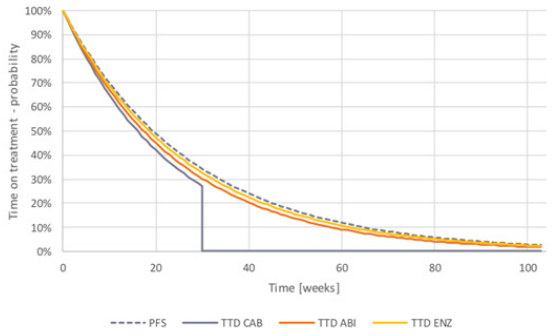

Chart 3. Comparison of TTD and PFS curves for all interventions

7. The average treatment duration was estimated in a 2-year time horizon. After two years, the percentages of patients continuing therapy with enzalutamide and abiraterone acetate are relatively low and amount to 2.1% and 1.6%, respectively. Adopting a shorter time horizon would result in underestimating the duration of treatment with abiraterone acetate and enzalutamide, for example after one year (i.e. after the horizon adopted in the analysis submitted to the AOTMiT), the percentage of patients continuing therapy (according to the adopted curves) is 12.6% and 14.3%, respectively for abiraterone acetate and enzalutamide.

The estimated mean treatment duration in a 2-year time horizon is:

- for cabazitaxel: 125 days (6 cycles),
- for abiraterone acetate: 187 days (6.1 months),
- for enzalutamide: 198 days (6.5 months).

8. In line with the recommendation included in the AOTMiT guidelines,[1] the selection of comparators to be compared with the assessed intervention should be based on clinical practice standards and guidelines, and the comparator for the assessed intervention should first and foremost be an existing medical practice, i.e. the intervention which will be replaced by the assessed technology. In view of the above, abiraterone acetate and enzalutamide were considered suitable comparators for cabazitaxel. Due to restrictions regarding the population which may benefit from radium 223 dichloride therapy and the actual small number of patients receiving it (compared to other therapeutic options), this technology should not be considered as an alternative procedure.

Therefore, the most reasonable approach is to set a threshold price in relation to the cost of using a "weighted comparator", understood as the average cost of abiraterone acetate and enzalutamide, weighted by shares of those therapies in clinical practice (in line with the assumptions adopted in the budget impact analysis, i.e. abiraterone acetate: 50%, enzalutamide: 50%). The statutory ex-factory price established for cabazitaxel is almost three times higher (increase by 169%) than the threshold price estimated in the AOTMiT's calculations. This price is the result of a realistic approach, reflecting the treatment guidelines in the analysed population and the actual market situation indicating a significant dominance of hormonotherapy in relation to radium 223 dichloride in terms of frequency of use. The "automatic" approach based on Article 13 of the Reimbursement Act, referring to the cheapest comparator, ignoring its actual share in sales, does not reflect the actual potential burden on the public payer's budget related to the possible reimbursement coverage of cabazitaxel.

Conclusions and discussion

The cost minimisation analysis seems to be a simple analysis which should be quickly accepted by decision makers in the reimbursement process. Currently in Poland cost minimisation analysis is required in cases when a difference in health effects cannot be demonstrated. However, in order for it to be properly used by the decision-maker, it should meet the basic assumption of reflecting the actual clinical reality. NICE guidelines[5, 6] and the Briggs article[2] recommend the cost minimisation analysis as a useful tool only in the case of obvious situations where there is evidence of lack of differences between the compared health interventions. Otherwise, a different type of economic analysis should be chosen. For the cost minimisation analysis to fully reflect the clinical reality (e.g. taking into account differences in drug dosage duration etc.), an economic model should be developed. In many situations, such a model can be very simplified.

In both assessed cost minimisation analyses, several limitations resulted in the AOTMiT's critical remarks or limit the usefulness of both analyses to the decision-maker. The CMA for cladribine tablets is characterised by limitations related to both the length of the time horizon and the calculation method. It seems that, in order to increase the usefulness of the analysis for the decision-maker, it would be necessary to extend the time horizon of the analysis to at least 10 years and to include any cases of early treatment discontinuation by patients in the analyses. However, the AOTMiT's comments in the verification analysis published on the website head in the opposite direction – they suggest shortening the time horizon of the analysis to 4 years. If the purpose of a CMA, in accordance with the AOTMiT guidelines, is to calculate the

differential cost of health interventions, the only solution is to extend the time horizon of the analysis.

In the case of the cost minimisation analysis for cabazitaxel, the identified limitations are:

- taking into account the same treatment durations for the compared health interventions (an approach proposed in the AOTMiT's verification analysis [9]) which resulted in the omission of the entire area related to differences in the type of treatment (chemotherapy, hormonotherapy), in particular treatment discontinuation due to the occurrence of adverse events and determining the maximum treatment duration for some interventions.
- using median treatment durations in the calculations, which led to the adoption of a one-year time horizon.

The article proposes a method which is free from the identified limitations.

Consideration of a drug which currently practically does not constitute a comparator in clinical practice leads to misguided conclusions, especially with regard to the threshold price.

A simple cost minimisation analysis, in which the maximum cost of therapy incurred in a given time is calculated, should be reserved only for obvious situations where actual differences can be demonstrated. If a cost minimisation analysis for more complex cases is developed, then it should be based on modelling both effects and costs in a similar way as a typical cost effectiveness/ cost utility analysis. The only difference will consist in the adoption of equal effectiveness of the compared health interventions.

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