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Treosulfan-based conditioning vs. low-dose busulfan-based conditioning for allogeneic hematopoietic stem cell transplantation: a cost-utility analysis in Poland

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Abstract

Introduction: In Poland, busulfan conditioning is used for allogeneic hematopoietic stem cell transplantation (allo--HSCT). Cost-utility analyses comparing alternative conditioning regimens in patients undergoing allo-HSCT have not been conducted so far.

Material and methods: A United Kingdom-based partitioned survival model was adapted to the Polish setting to compare treosulfan to low-dose busulfan conditioning regimen from the public payer's perspective in Poland. Patient characteristics, overall survival (OS), event-free survival (EFS), and the rate of adverse events were obtained from the randomized MC-FludT.14/L trial. Parametric survival models of up to 5 years (the cure threshold), with subsequent mortality defined using survival of the general population of Poland adjusted for cancer survivors, were used to extrapolate OS and EFS beyond the trial duration. Published utilities were adjusted for age using age-dependent general population utilities. The costs of treatment, adverse events, and inpatient/outpatient care were assessed via official remuneration schemes.

Results: Treosulfan-based conditioning outperformed low-dose busulfan, i.e. it was more effective with incremental quality-adjusted life years (QALY) of 0.78 and less expensive by 1,139 PLN per patient over the lifetime horizon. Deterministic sensitivity analyses revealed treosulfan was highly cost-effective (i.e. incremental cost-utility ratio was lower than the gross domestic product per capita in Poland) compared to low-dose busulfan, if most uncertain parameters are changed or alternative scenarios are implemented. The probability of treosulfan being cost-effective with a threshold of 155,514 PLN was 99.6%.

Conclusions: Compared to low-dose busulfan, treosulfan is a highly cost-effective conditioning regimen for allo-HSCT patients ineligible for standard conditioning regimens.

Key words: cost-effectiveness, cost-utility, treosulfan, busulfan, hematopoietic stem cell transplantation

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Introduction

Myelodysplastic syndrome (MDS) is a group of diverse bone marrow abnormalities associated with ineffective hematopoiesis, which manifest as morphologic dysplasia as well as ineffectual production of blood cells resulting in peripheral blood cytopenias. The incidence of MDS is approximately 3–4 cases/100,000, with about 20,000 cases annually being high risk. However, it should be stressed that the actual incidence of this disease could be significantly higher due to its nonspecific symptoms, which often include anemia, fatigue, weakness, intolerance of physical exertion, angina, as well as cognitive impairment [1–3]. Due to its symptom burden, MDS significantly negatively affects quality of life. Moreover, it can be associated with a high social and economic burden, as well as significant utilization of health care funds [3]. In many patients, especially those with indolent or rapidly progressive MDS, along with those with complications secondary to profound cytopenias, myelodysplastic syndrome can progress to acute myeloid leukaemia (AML) [2, 3]. AML consists of multiple clonal hematopoietic disorders which result in proliferation of immature myeloid cells in the bone marrow. Accumulation of the leukemic blasts of myeloid lineage leads to an impairment of hematopoietic function, which results in the occurrence of cytopenias, with or without leucocytosis [3]. Acute myeloid leukaemia is the most common form of adult acute leukaemia, with 18,860 diagnosed cases and 10,460 deaths in the USA in 2014 [4].

Allogeneic hemopoietic stem cell transplantation (HSCT) plays a crucial role in the management of adult patients with myelodysplastic syndrome or acute myeloid leukemia [5, 6]. In fact, these two diseases account for more than half of the HSCT indications for malignant diseases worldwide, while in the USA alone in 2010, AML was the most common indication for this procedure [5, 7]. This is because, to date, hemopoietic stem cell transplantation remains the only curative treatment for acute myeloid leukemia and intermediate-to-high-risk myelodysplastic syndrome [3, 8]. However, HSCT itself can be associated with a plethora of significant adverse events, as well as increased treatment-related mortality [7]. Therefore, before allogeneic hematopoietic stem cell transplantation, it is necessary for patients to undergo conditioning treatment aimed at eradicating disease remnants and weakening the recipient's immune system [9].

For this purpose, myeloablative therapy is used, which usually uses high-dose cyclophosphamide in combination with whole-body radiotherapy or high-dose busulfan. Nevertheless, due to the relatively high toxicity, as well as veno-occlusive diseases, and significant risk of mortality after such therapy, it can only be used by relatively young patients (up to 50–55 years of age) who are in good general condition. Older patients, as well as those in poor general condition, with lower performance status, and greater burden of comorbidities, may be referred to a lower-intensity conditioning treatment, usually involving lower doses of intravenous busulfan and an infusion of fludarabine [3, 10]. However, using the reduced-intensity conditioning can be problematic, because such a regimen, aimed to induce sufficient immunosuppression to enable engraftment, mostly relies on the graft-versus-malignancy effect for the curative results. Therefore, conditioning treatments of reduced intensity are associated with a higher risk of relapse compared to standard regimens. This is a significant limitation and poses a major obstacle to successful transplantation [11].

Therefore, the current development of preparative regimens before allogeneic HSCT is addressing an unmet medical need for the growing number of patients with myelodysplastic syndrome or acute myeloid leukemia. Providing better access to the therapy for patients would seem to be crucial in order to improve clinical outcomes [5] It is a particularly significant unmet need because myelodysplastic syndrome is usually diagnosed among older adults (80% of adult diagnosed patients are ≥70 years), while the diagnosis of acute myelogenous leukemia most often happens between the ages of 68 and 72. Additionally, considering the phenomenon of population ageing, it can be assumed that both MDS and AML in years to come will be ever more frequently encountered in geriatric practices [3, 5].

A conditioning treatment prior to allogeneic hematopoietic cell transplantation that could be used in older patients is treosulfan therapy in combination with fludarabine. The results of a study [5] indicate that the effectiveness of this therapy may be even higher than the standard of conditioning treatment with reduced activity [5], but therapy with intravenous busulfan and fludarabine is unavailable in Poland. Currently, treosulfan is not financed from public resources in Poland. Among the drugs containing the active substance treosulfan, the drugs authorized in Poland are powders for solution for infusions: treosulfan (5 g and 1 g in 50 mg/mL; 1 or 5 vials) [12, 13].

So we performed a cost-utility analysis to compare treosulfan and fludarabine conditioning to low-dose busulfan and fludarabine-based conditioning prior to allogeneic hematopoietic stem cell transplantation (allo-HSCT) in patients considered ineligible for standard conditioning regimens in Poland.

Material and methods

A partitioned survival model developed for a UK setting and positively appraised by the Evidence Review Group (ERG), commissioned by the National Institute for Health and Care Excellence (NICE) [14], was adapted to a Polish setting by the inclusion of input data specific to patients from Poland. In the model, patients started in the induction/allo-HSCT health state, before transitioning to allo-HSCT recovery

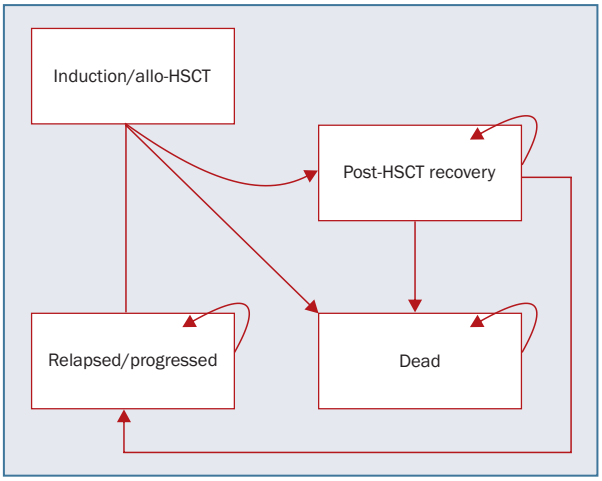

Figure 1. Model diagram; allo-HSCT — allogeneic hematopoietic stem cell transplantation

(remission), relapse/progression/graft failure, and/or death after the first model cycle (Figure 1). A cycle length of 28 days and half-cycle correction were applied. The time horizon was a lifetime (50 years). The costs and QALYs were discounted by 5.0% and 3.5% annually, respectively.

The population was the same as in the MC-FludT.14/L trial [5], which was a randomised non-inferiority phase 3 trail in 31 transplantation centres in France, Germany, Hungary, Italy, and Poland. Eligible patients were 18–70 years, had acute myeloid leukaemia in first or consecutive complete haematological remission (blast counts <5% in bone marrow and included patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) considered ineligible for standard conditioning regimens before allo-HSCT. The regimens were as follows: intravenous treosulfan at a dose of 10 g/m^2 of body surface area daily for 3 days and intravenous busulfan at a dose of 0.8 mg/kg every 6 hours (or 3.2 mg/kg daily) for 2 days, both with 30 mg/m^2 of intravenous fludarabine daily for 5 days.

Data on patient characteristics, overall survival (OS), event-free survival (EFS), and adverse events [stage III/IV acute and extensive chronic graft-versus-host disease (GvHD), other grade 3+ adverse events with ≥1% incidence in either treatment arm] were collected from the MC-FludT.14/L trial. Parametric survival models were used to extrapolate OS and EFS beyond the trial duration. Standard parametric models, commonly used (Weibull, lognormal) mixture-cure models (MCM), and commonly used (Weibull, lognormal) non-mixture-cure models (NMCM) were fitted to the full survival datasets from the MC-FludT.14/L trial. Survival analyses were conducted for the pooled AML and MDS cohorts, as well as separately for the AML and MDS subpopulations stratified by treatment arm. For consistency, the same model type was used for each arm both for treosulfan and busulfan [15]. The NMCM log-normal distribution for EFS and NMCM Weibull distributions for OS were selected in a base-case analysis on the basis of their statistical fit (Akaike information criterion), visual inspection, and clinical validity. The base-case model used an extrapolation method selected by the Evidence Review Group in the UK [5]. Five different variants of long-term extrapolation were considered: 1) parametric models fitted to trial data; 2) parametric models or general population life tables, depending on which had the higher mortality rate; 3) parametric models or standardized mortality ratio (SMR)-adjusted general population life tables, depending on which had the higher mortality rate; 4) parametric models up to a cure threshold, followed by a switch to general population life table mortality rates; and 5) parametric models up to a cure threshold, followed by a switch to SMR-adjusted general population life table mortality rates. The latter variant was considered in a base-case analysis as allo-HSCT is a potentially curative treatment: the relapse rate after 5 years is minimal according to clinical experts and the assumption was incorporated in other economic evaluations on the topic [5]. Prior to the cure threshold, the parametric curves for OS and EFS were used. After the cure threshold, mortality was determined by using life tables for the general population [16] adjusted with SMR for HSCT (2.3. calculated in [17] based on data from Martin et al. [18]). In the base case analysis, the cure threshold was assumed to be 5 years post-HSCT, as patients surviving allo-HSCT for at least 5 years are considered to be cured in clinical practice.

Quality-of-life data was not collected during the MC-FludT.14/L trial. Therefore, health-related utilities were sourced from published studies. For estimating post-HSCT recovery utility, data from Grulke et al. 2012 [19] was mapped to the utilities using an algorithm by Proskorovsky et al. 2014 [20] (data from Castejon et al. 2018 [21] were used in a scenario analysis). Relapse/progression and adverse event utilities were based on previous models submitted to the NICE [22], while disutilities for graft-versus-host disease events were obtained from Kurosawa et al. 2016 [23] with the assumption that disutilities for grade 3–4 acute GvHD are the same as for chronic GvHD. The utilities were adjusted according to the difference in the mean age of patients in studies used for utility calculation and the mean age of patients at baseline in the MC-FludT.14/L trial (59.6 years) as well as during each cycle of the time horizon. The adjustment was made with age-dependent utilities of the general Polish population [24].

Detailed information on the original model is available in the studies by Westwood et al. [14] and Bungey et al. [25].

The economic analysis was conducted from a public payer's perspective, i.e. the National Health Fund (*Narodowy Fundusz Zdrowia* or NFZ in the Polish acronym). Conditioning treatments are not directly financed from public funds in Poland. The NFZ does not directly finance

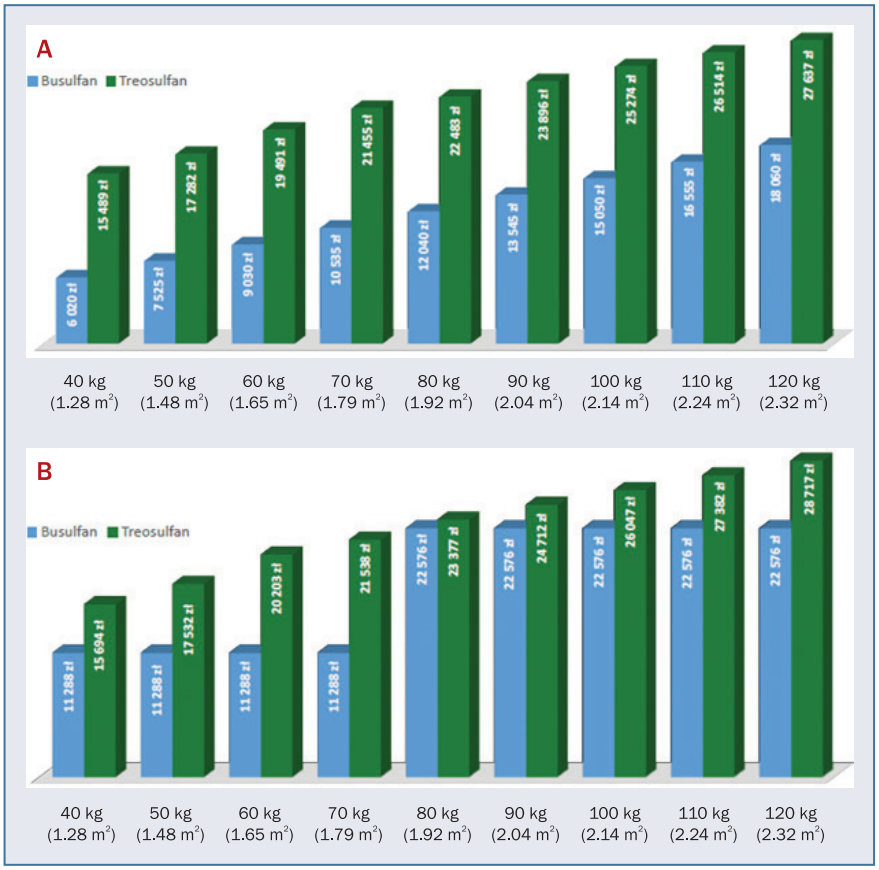

Figure 2. Comparison of treosulfan and low dose busulfan costs per patient by body weight and body surface area: cost of drug administered to patient without cost of unused portion of vial, i.e. scenario without wastage (**A**); cost of drug administered to patient and cost of unused portion of vial with assumption that 100% of unused drug is disposed of, i.e. scenario with full wastage (**B**)

treosulfan, busulfan, and fludarabine used in this indication. Polish hospitals buy these drugs from the funds allocated to diagnosis-related groups [in Polish: *jednorodne grupy pacjentów* (JGP)] designed for allo-HSCT (i.e. JGP S22 'Transplantation of allogeneic hematopoietic cells from siblings identical in HLA' or S23 'Transplantation of allogeneic hematopoietic cells from an alternative donor'). The JGPs are designed to cover the costs of mobilization, conditioning, transplantation, and post-transplant hospitalization up to 30 days, with an additional cost for each day of inpatient stay beyond 30 days. Because of the difference in the total costs of treosulfan and busulfan treatment (treosulfan has a higher acquisition cost compared to low-dose busulfan, Figure 2), and lack of direct reimbursement from the public purse (the hospital acquires these drugs using the funds allocated to the allo-HSCT procedure), treosulfan is not commonly used in Poland.

To assess whether the higher price of treosulfan vs. low-dose busulfan is justified, we assumed that the NFZ would directly finance the cost of treosulfan, while busulfan and fludarabine would not be separately financed by the NFZ. Hence, in the base-case analysis, the cost of conditioning treatment and allo-HSCT included: 1) the cost of treosulfan and allo-HSCT (JGP S22 or S23) in the treosulfan arm; and 2) the cost of allo-HSCT alone (JGP S22 or S23) in the busulfan arm. The remaining costs (i.e. adverse events, post-HSCT care, disease relapse/progression) were the same for both arms, while only the risk of these events differed between the arms.

The cost of treosulfan and busulfan was based on average gross wholesale prices in Poland (445.07 PLN and 1,948.05 PLN for 1,000-mg and 5,000-mg vials of treosulfan, respectively; 1,410.97 PLN for a 60-mg vial of busulfan). The cost of allo-HSCT procedure was based on the current unit cost of JGP S22 or S23 [26] and related statistics in 2019 (number of patients and length of hospital stay for each JGP) [27]. The average cost of allo-HSCT with healthcare provided up to 42.1 days after the admission to hospital for allo-HSCT was 237,865.89 PLN. The cost of drugs used for disease relapse/progression was estimated based on the average unit price of those drugs in 2020 [28] with utilization obtained from the original model [5, 25] (based on treatment guidelines and clinical expert opinions, with the usage assumed to be equally distributed among patients relapsing/progressing in the first year as well as patients relapsing/progressing after

Table I. Main inputs for base-case model

Parameter	Value	Source
Age (mean) [years]	59.6	MC-FludT.14/L trial
Weight (mean), kg/body surface area [m^2]	80.2/1.93	
Matched unrelated donor [%]	76.4%	
Sex (male) [%]	60.8%	
Cure threshold	5 years	Assumption
SMR after cure threshold	2.3	Martin 2010 [21]
Utility of induction/allo-HSCT	0.558	Grulke et al. 2012 [22] (algorithm by Proskorovsky et al. 2014 [23]) adjusted with data from [27]
Post-HSCT recovery utility: discharge	0.660	
Post-HSCT recovery utility: ≤6 months	0.756	
Post-HSCT recovery utility: 7–12 months	0.818	
Post-HSCT recovery utility: year 2	0.822	
Post-HSCT recovery utility: year 3	0.822	
Post-HSCT recovery utility: year 4+	0.870	
Relapse/progression	0.623	[25] adjusted with data from [27]
Graft-versus-host disease disutility	–0.120	[26]
Grade 3+ adverse events disutility	–0.024	[25]
Cost of allo-HSCT with treatments and care up to 42.1 days after procedure: treosulfan arm	261,507.71 PLN (with total cost of treosulfan at 23,376.60 PLN included)	Data from selected drug wholesalers on treosulfan price [29–31], assumption
Cost of allo-HSCT with treatments and care up to 42.1 days after procedure: busulfan arm	240,583.59 PLN without separate cost of busulfan	[29–31]
Cost of allo-HSCT recovery/remission — <12 months	2,448.56 PLN per cycle	[29, 30, 32]
Cost of allo-HSCT recovery/remission — 12–24 months	2,031.64 PLN per cycle	[29, 30, 32]
Cost of allo-HSCT recovery/remission — >24 months	83.38 PLN per cycle	[29, 30, 32]
Cost of early relapse/progression (<12 months)	5,094.91 PLN per cycle*	[18–30, 32]
Cost of late relapse/progression (≥12 months)	120,291.79 PLN per 1st cycle, 4,552.34 PLN per cycle**	[18–30, 32]
End-of-life cost	7,197.94 PLN per event	[32]
Additional cost of graft-versus-host disease	17,593.00 PLN per event	[32]
Grade 3+ febrile neutropenia, lung infection, or syncope	10,440.00 PLN per event	Assumption [29, 32]
Grade 3+ sepsis	11,789.00 PLN per event	Assumption, [29]
Grade 3+ other adverse events	71.00 PLN per event	Assumption [29, 32]

*Assumes equal probability of receiving hypomethylating agents (azacitadine), salvage chemotherapy [etoposide + cytarabine + mitoxantrone (MEC)] and palliative chemotherapy (hydroxycarbamide) treatment regimens; **assumes equal probability of receiving FLAG/Ida [fludarabine + cytarabine + granulocyte colony-stimulating factor (G-CSF)/idarubicin) or secondary allo-HSCT. Secondary allo-HSCT costs applied as one-off cost in first cycle of relapse/progression; SMR — standardized mortality ratio; allo-HSCT — allogeneic hematopoietic stem cell transplantation

1 year based on clinical experts agreeing to that assumption). The cost of outpatient and inpatient procedures was estimated using official unit prices [26] with their shares obtained from data on incidence in 2019 in Poland and/or data presented in other economic analyses submitted to the Agency for Health Technology Assessment and Tariff System in Poland [29].

The main model's inputs are presented in Table I.

The primary outcomes of the analysis included: 1) the incremental cost-utility ratio (ICUR), estimated in terms of the cost per quality-adjusted life year (QALY), which was compared to the threshold of 3 x the gross domestic product per capita in Poland (155,514 PLN in 2021); 2) the incremental net monetary benefit (INMB) expressed as: $INMB = WTP \times \Delta QALY - \Delta C$, where WTP is the threshold, while $\Delta QALY$ and ΔC denote a difference between arms in QALYs and total costs, respectively. When the INMB is higher than or equal to zero, this indicates that the treatment is cost effective, with the willingness to pay per additional QALY at 155,514 PLN. Costs were expressed in PLN (€1 =

Table II. Results of base-case analysis

Parameter	Treosulfan	Busulfan	Incremental
Mean event-free survival, years	9.84	7.96	1.87
Mean overall survival, years	10.51	9.27	1.23
Life years (discounted)	7.85	6.94	0.91
QALY (discounted)	5.74	4.96	0.78
Cost of treosulfan/busulfan	23,377 PLN	0 (included in cost of HSCT procedure)	23,377 PLN
Cost of HSCT procedure (including fludarabine, busulfan and others)	238,131 PLN	240,584 PLN	–2,453 PLN
Cost of healthcare after HSCT (discounted)	44,858 PLN	40,545 PLN	4,313 PLN
Cost of adverse events treatment (discounted)	3,904 PLN	4,453 PLN	–549 PLN
Cost of event-free survival (discounted), overall	309,290 PLN	284,680 PLN	24,610 PLN
Cost of relapsed/progressed disease (discounted)	19,831 PLN	44,725 PLN	–24,895 PLN
End-of-life cost (discounted)	5,464 PLN	6,319 PLN	–854 PLN
Total cost (discounted)	334,585 PLN	335,724 PLN	–1,139 PLN
ICUR	–	–	Dominant
INMB	–	–	122,764 PLN

QALY — quality-adjusted life year; HSCT — hematopoietic stem cell transplantation; ICUR — incremental cost-utility ratio; INMB — incremental net monetary benefit

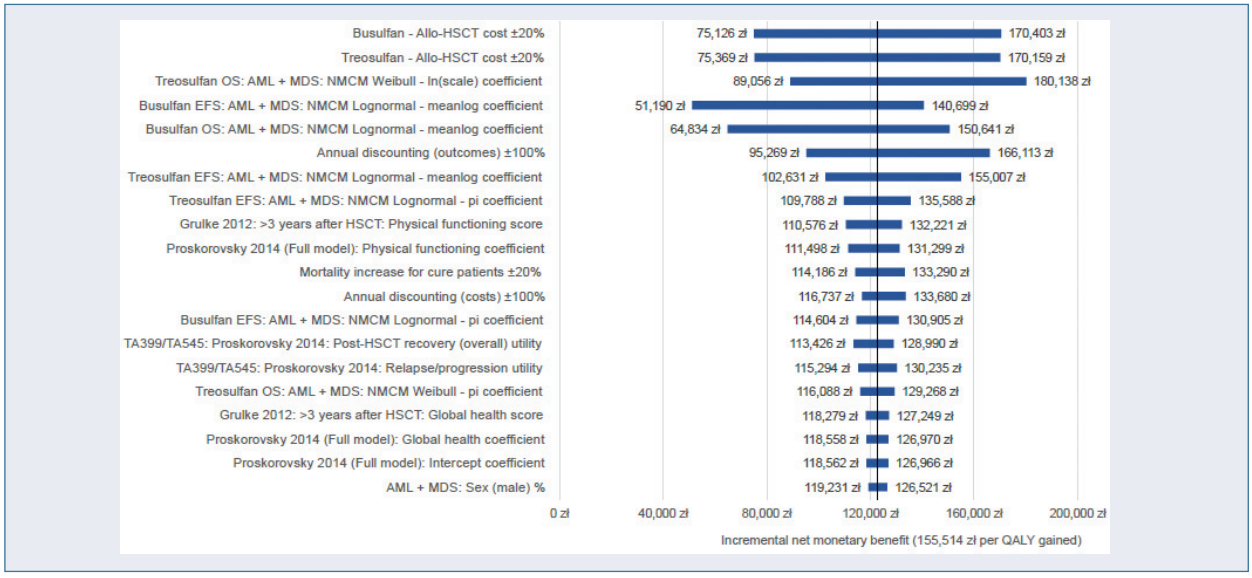

Figure 3. Tornado diagram for deterministic sensitivity analyses; allo-HSCT — allogeneic hematopoietic stem cell transplantation; OS — overall survival; AML — acute myeloid leukemia; MDS — myelodysplastic syndrome; NMCM — non-mixture-cure models; EFS — event-free survival

= 4.47 PLN). The study was reported in adherence with the Consolidated Health Evaluation Reporting Standards [30] and Polish guidelines [31].

One-way deterministic sensitivity analyses were performed for all parameters. Additionally, the alternative source or assumption was tested via scenario analyses, which included optional extrapolation distributions and scenarios (with or without the cure threshold), optional sources of utilities, and optional assumptions regarding the cost of treosulfan and/or busulfan (e.g. with treosulfan-only cost that exceeded busulfan cost financed by the NFZ, without treosulfan wastage, with treosulfan financed by the NFZ: with full wastage, without wastage, or with partial wastage, which assumed that only the unused part of the last vial is dispensed with).

A probabilistic sensitivity analysis, based on 5,000 sets of randomly drawn input parameters, was carried out to calculate the confidence intervals around the base-case

Table III. Results of scenario analyses

Parameter	Incremental QALY	Incremental costs	ICUR (PLN/QALY gained)	INMB
Base-case analysis	0.78	–1,139 PLN	Dominant	122,764 PLN
AML subpopulation only	0.71	–12,545 PLN	Dominant	123,095 PLN
MDS subpopulation only	0.89	11,557 PLN	13,051 (<155,514)	126,145 PLN
Pooled separate modelling for AML and MDS patients	0.77	–3,840 PLN	Dominant	124,196 PLN
Without cost of treosulfan wastage	0.78	–2,001 PLN	Dominant	123,626 PLN
EFS and OS extrapolation: variant 1	1.35	–26,907 PLN	Dominant	236,329 PLN
EFS and OS extrapolation: variant 2	0.97	–9,559 PLN	Dominant	161,115 PLN
EFS and OS extrapolation: variant 3	0.79	2,777 PLN	3,532 PLN (<155,514)	119,502 PLN
EFS and OS extrapolation: variant 4	0.99	–7,725 PLN	Dominant	161,301 PLN
EFS model: gamma	0.75	9,504 PLN	12,743 PLN (<155,514)	106,481 PLN
EFS model: MCM lognormal	0.79	–1,655 PLN	Dominant	123,779 PLN
EFS model: Gompertz	0.78	1,505 PLN	1,934 PLN (<155,514)	119,533 PLN
OS model: gamma	0.75	–3,726 PLN	Dominant	120,594 PLN
OS model: MCM Weibull	0.79	–709 PLN	Dominant	123,242 PLN
OS model: MCM Lognormal	0.78	–1,162 PLN	Dominant	121,731 PLN
OS model: NMCM Lognormal	0.78	–770 PLN	Dominant	121,790 PLN
Cure threshold: 3 years	0.82	12,377 PLN	15,090 PLN (<155,514)	115,177 PLN
Cure threshold: 7 years	0.79	–5,879 PLN	Dominant	129,425 PLN
Busulfan directly financed by NFZ with partial cost of wastage	0.78	–13,855 PLN	Dominant	135,480 PLN
Busulfan directly financed by NFZ with full cost of wastage	0.78	–23,745 PLN	Dominant	145,371 PLN
Only treosulfan cost that exceeds busulfan cost financed by NFZ	0.78	–13,790 PLN	Dominant	135,415 PLN
Post allo-HSCT utilities from Castejon et al. 2018	0.64	–1,139 PLN	Dominant	100,596 PLN

QALY – quality-adjusted life year; HSCT – hematopoietic stem cell transplantation; ICUR – incremental cost-utility ratio; INMB – incremental net monetary benefit; AML – acute myeloid leukemia; MDS – myelodysplastic syndrome; EFS – event-free survival; OS – overall survival; MCM – mixture-cure models; NMCM – non-mixture-cure models; NFZ (*Narodowy Fundusz Zdrowia*) – National Health Fund

analysis results and to calculate the probability of treosulfan being cost-effective.

Results

The base-case model indicated that patients receiving the treosulfan conditioning regimen did not experience cancer-related events for an additional 1.87 years compared to patients receiving a low-dose busulfan conditioning regimen. Moreover, the mean OS was prolonged by 1.23 years.

Compared to busulfan, treosulfan-based conditioning led to a gain of 0.78 QALYs with a reduced cost of 1,139 PLN per patient.

The results indicate that treosulfan outperforms busulfan in Poland, in that it is more effective and less expensive (Table II).

The sensitivity analyses confirmed the results of the base-case analysis. Neither the change of any model parameter (Figure 3) nor the implementation of any scenario (Table III) affected the cost-effectiveness of treosulfan at a threshold of 155,514 PLN per QALY gained. Treosulfan was either dominant or highly cost effective (i.e. ICUR less than the gross domestic product per capita in Poland) compared to low-dose busulfan. Of the model parameters and extrapolation variants, the allo-HSCT cost, EFS, and OS had the greatest impact on the results.

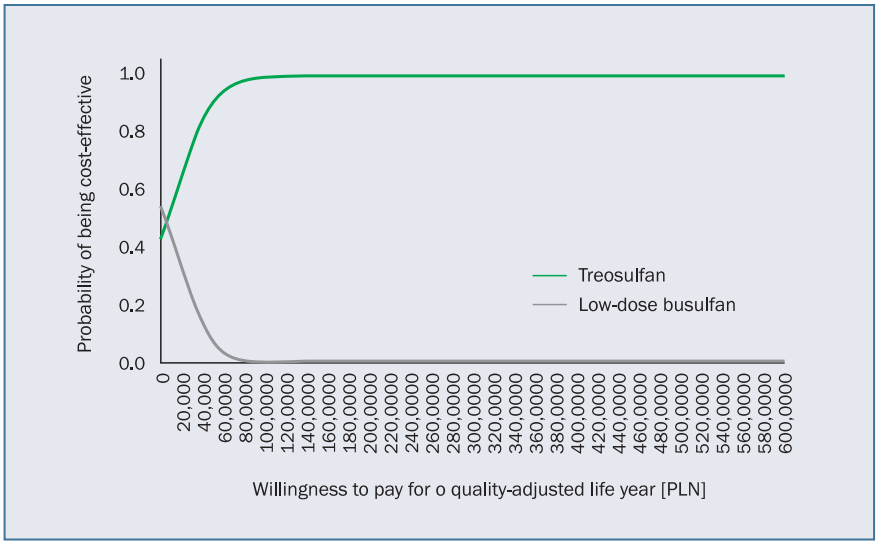

Figure 4. Cost-effectiveness acceptability curve

The probabilistic sensitivity analysis indicated a probability of 99.6% for treosulfan being cost-effective at a threshold of 155,514 PLN per QALY gained (Figure 4).

Discussion

Treosulfan is an alkylating agent viewed as a well-tolerated alternative to other chemotherapy drugs (including other alkylating agents) in conditioning regimens for allo-HSCT; in combination with fludarabine, it is indicated as part of conditioning treatment prior to allo-HSCT in adult patients with malignant and non-malignant diseases, and pediatric patients older than one month with malignant diseases [13]. It is also important to stress that, as demonstrated in a recently published meta-analysis, treosulfan is characterized by a strong activity against AML cells, as well as strong immunosuppressive effects, but is associated with low release of inflammatory cytokines.

These qualities promote the engraftment of the transplanted cells while limiting the risk of GvHD [8]. Additionally, the safety and clinical effectiveness of treosulfan-based regimens as a conditioning treatment have also been confirmed in a dose-escalation study carried out among patients with a variety of hematological malignancies, as well as research including patients with a high risk of both regimen-related toxicity and graft failure [11].

Therefore, thanks to the described characteristics, treosulfan-based regimens are considered to have effectiveness analogous to, or better than in the case of overall survival, conventional myeloablative conditioning regimens, with lower risks of toxicity, the occurrence of GvHD, and transplant-related mortality [8].

This makes treosulfan-based conditioning a great option for patients who are not well enough for standard conditioning, and gives them a chance to undergo a potentially curative procedure.

High clinical effectiveness of treosulfan-based conditioning regimens has also been demonstrated in a pivotal clinical study that aimed to evaluate the efficacy and safety of conditioning with treosulfan plus fludarabine compared to reduced-intensity busulfan plus fludarabine in patients with acute myeloid leukemia or myelodysplastic syndrome. Patients included in the study were at an increased risk of adverse events with the use of standard conditioning therapies because of their older age (≥50 years) or comorbidities [Hematopoietic Cell Transplantation—Comorbidity Index (HCT-CI) score >2]. In this study, 2-year event-free survival reached 64% [95% (CI, confidence interval) 56–70.9] in the treosulfan group and 50.4% (42.8–57.5) in the busulfan group [hazard ratio (HR) 0.65 (95% CI 0.47–0.90)]. The most frequently reported adverse events of grade 3 or higher included abnormal blood chemistry results [33 (15%)/221 for the treosulfan group vs. 35 (15%)/240 patients in the busulfan group] as well as gastrointestinal disorders [24 (11%) vs. 39 (16%) patients]. Serious adverse events were observed in 18 (8%) patients in the treosulfan cohort and in 17 (7%) in the busulfan group. Deaths noted during the study were, generally, transplantation-related [5].

The described study has several significant strengths, which should be pointed out. These include the randomization and multicenter character of the study, as well as a fairly large population of patients included in the study (476 patients). Additionally, due to the open-label model, the researchers decided to choose a robust primary endpoint, which was as independent as possible from the subjective view of both the patient and the investigator. Moreover, investigators and other personnel included in the research were blinded to aggregated data analyses

until database lock. This reduced the risk of bias associated with lack of blinding, which was one of the most significant limitations of the study. Other limitations included the limited use of disease-specific risk scores, such as the disease risk index to adjust for transplantation-related risks, as well as not implementing measurable residuals as the disease-independent prognostic indicator for the post-transplant relapse risk [5].

Despite these limitations, the results of the described clinical study provide important information regarding the conditioning treatment of patients who are not fit for standard regimens utilized before allo-HSCT. They allow us to conclude that treosulfan is non-inferior to busulfan when used in combination with fludarabine as a conditioning treatment utilized before allo-HSCT for patients with acute myeloid leukemia or myelodysplastic syndrome, who are elderly and/or have significant comorbidities which have made the use of standard conditioning treatments impossible.

These findings suggest that treosulfan-based regimens have significant potential to become the standard preparative regimen among such patients [5].

Our study confirms that the conditioning regimen with treosulfan instead of low-dose busulfan is highly cost effective in Poland. However, the analysis has several major limitations. Firstly, there may be differences in the characteristics of patient populations in the included studies [5, 19, 20, 23]. Secondly, efficacy data is limited due to a relatively short duration of the clinical trial (up to 1,586 days) which was used to inform the model during the lifetime horizon. Nevertheless, optional extrapolation variants and survival models did not change the conclusion from the base-case analysis. Thirdly, the cost input was based on other economic analyses or assumptions because valid cost data on Polish patients was unavailable. Finally, the utilities were sourced from published studies, as quality-of-life data was not collected during the MC-FludT.14/L trial.

Only a single economic study of treosulfan-based conditioning in allo-HSCT patients was identified, namely the original model with UK-specific data [5, 25]. Our results are similar to those obtained in that original model, which may indicate that cost inputs and other country-specific input data do not affect the overall conclusion from the cost-effectiveness point of view. Also in regards to the analysis in the subgroups based on the diagnosis (AML and MDS separately), our obtained results (QUALY 0.71 for AML and 0.89 for MDS) were similar to the findings of the UK study (QUALY 0.71 for AML and 1.03 for MDS) [25].

Therefore, it can be concluded that, in both countries, treosulfan-based regimens are a highly cost-effective conditioning treatment for patients with AML or MDS who can benefit from undergoing allo-HSCT, but who are ineligible for standard conditioning regimens.

Based on the available data, as well as the results of the present study, it can be concluded that myeloablative properties and high cytotoxic activity on hematopoietic cells of treosulfan-based regiments, combined with their low non-hematological toxicity, can significantly improve the survival of patients with myelodysplastic syndrome as well as acute myeloid leukemia. This applies especially to elderly patients, as well as those in poor general condition, with lower performance status and a greater burden of comorbidities. Moreover, it should be stressed that such conditioning regimens are associated with a lower incidence of acute graft-versus-host disease compared to busulfan-based treatment. Additionally, and especially importantly from the socio-economic perspective, treosulfan-based conditioning is highly cost-effective in Poland.

Conclusions

The results of this study indicate that compared to low dose busulfan, treosulfan-based conditioning for allo-HSCT patients with AML or MDS ineligible for standard conditioning regimens is highly cost-effective in Poland.

Authors' contributions

PK, PH — conceived and designed model adaptation. PH — performed analysis and generated figures. GB, OM — designed and constructed original model. PH, MZ — prepared first draft. PK, MM — critically reviewed and edited paper. All authors contributed to and accepted final version of manuscript.

Conflict of interest and financial support

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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