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Decision Analysis of Treatment Strategies in Children with Severe Sickle Cell Disease

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Abstract

We designed a decision analysis model comparing four treatment strategies for severe sickle cell disease: no intervention, hydroxyurea, chronic transfusion, or stem cell transplant. The treatment strategy associated with the highest average utility (quality of life) was stem cell transplant (0.85). Average utilities for no treatment, chronic transfusion, and hydroxyurea were 0.68, 0.71, and 0.80, respectively. Our model was quite sensitive to quality of life estimates, indicating that a true comparison of hydroxyurea and transplantation cannot occur until investigators directly measure the health-related quality of life in children with sickle cell disease during hydroxyurea therapy and after stem cell transplant.

Keywords

Sickle cell disease; sickle cell anemia; decision analysis; decision making; quality of life

INTRODUCTION

Sickle cell disease (SCD) is a genetic disease in which the substitution of a single amino acid causes the production of the abnormal hemoglobin S. Despite a common genotype, there is a large degree of clinical variability in the pattern and severity of disease manifestations. Patients with a history of sickle cell-related complications, such as recurrent acute chest syndrome and three or more episodes of vaso-occlusive events within 12 months have been classified as having severe disease in previous clinical trials for adult and pediatric patients with SCD [1-3].

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To date, three interventional treatments have been separately tested and shown to be effective in decreasing the acute and long-term complications of sickle cell disease: hydroxyurea therapy, chronic transfusions, and hematopoietic stem cell transplantation [1, 3, 4]. These treatments have different efficacy and toxicity rates, but no randomized studies have been conducted to compare them directly. Because of the variation in risk-benefit profiles for each intervention, there is little consensus among sickle cell clinicians when recommending a therapy.

When definitive answers from randomized clinical trials are not available to answer a clinical question, decision analysis can be used as a tool in medical decision making. In this simulation model-based technique, an investigator combines information from a variety of sources to create a mathematical model representing a clinical decision [5]. First, the investigator structures the clinical problem as a decision tree representing the temporal sequence of possible clinical events. Next, data are collected to estimate the probability of each event, as well as the expected risks, benefits, and sometimes costs of each strategy. The decision tree is then analyzed to identify which strategy has the highest expected value, and is therefore the preferred course of action. The probabilities for an outcome or health state should be estimated from the best available information source, such as a significant clinical trial published in the area.

Decision analysis can also consider the patient's individual preference for a health state (utility). Health state utilities are usually assessed relative to two extremes, referred to as anchor states. Commonly used anchor states are "death," assigned value of 0, and "live in perfect health", assigned value of 1. Utility can be estimated or measured. Estimation can be performed in three different ways: arbitrarily assigning values based on an expert's judgment, asking a group of experts to reach a consensus, or searching for relevant published utility values in the literature. Utility can be directly measured in subjects using reliable and valid techniques such as time-trade off, standard gambling, and visual analog scales [6]. Utility can also be measured using preference-based quality of life inventories such as the Health Utility Index or the EuroQol-5D.

Few decision analysis studies have been published in sickle cell disease. Mazumdar et al explored the optimal frequency of transcranial Doppler screening [7]. Nietert et al compared stem cell transplant to periodic blood transfusions in patients with abnormal transcranial Dopplers [8]. Our objective was to develop a preliminary decision analysis model for pediatric patients with severe sickle cell disease due to recurrent vaso-occlusive events to identify key variables of interest to guide future research. The model takes into account current knowledge of treatment risks and benefits for the three available treatments for sickle cell disease (hydroxyurea, chronic transfusions, and stem cell transplantation) as well as estimated patient preferences for health states.

MATERIALS AND METHODS

As reviewed by Burd and Sonnenberg, there are four basic steps to applying decision analysis to a given clinical dilemma [5]. These steps include: 1) identify and define the scope of the problem, 2) structure the problem in the form of a decision tree, 3) collect data

to estimate the probability of each event and quantify outcomes, and 4) analyze the decision tree to determine the preferred course of action.

Identify and define the scope of the problem

In decision analysis, it is critical to precisely define both the patient population under study, and the clinical strategies being compared. In our model, the study population was comprised of patients with clinically severe SCD followed over a five-year time period. Although the appropriate definition of severe SCD remains debated within the field, we chose a definition used in previously published multicenter studies of hydroxyurea and stem cell transplant [1-3, 9]. Therefore, severe disease was defined as patients with HbSS or HbS β^0 thalassemia and ≥ 2 acute chest syndrome events in a two-year period, ≥ 3 pain episodes requiring emergency room visit or hospital admission in a 12-month period, or a combination of any of the two totaling 3 episodes in a 12-month period. The clinical decision in our model involves a choice between 1) no intervention, 2) hydroxyurea (HU), 3) chronic transfusion (CTX), and 4) stem cell transplant (SCT).

Constructing the decision tree

Once the study population and problem are defined, the problem is structured in the form of a decision tree (Figure 1). The square node represents the decision to choose one of four possible treatment strategies. Once the strategy has been chosen, subsequent events occur by chance, and are called "chance nodes" represented by circles, such as the chance of developing graft versus host disease after a stem cell transplant. At the end of each tree branch is a terminal node (represented by a triangle) which represents the health outcomes associated with the full sequence of events in that pathway. In this model, the health outcome of interest was quality-adjusted life-years (QALYs). We constructed and analyzed our model using TreeAge Pro Suite 2008 (TreeAge, Williamstown, MA).

Estimating probabilities and outcome measures

Model estimation involves assigning estimates for clinical probabilities and quality of life measures to each branch of the decision tree. Usually the exact value cannot be estimated with certainty. Therefore, the value that is believed to be the best estimate is used in the base case analysis. We obtained probabilities for most health states from a literature search using PubMed and OVID search engines. The following key words were used: sickle cell disease, hydroxyurea, chronic transfusion, stem cell transplant, mortality, side effects, pediatrics, children, iron overload, GVHD, and graft failure. Five- year probabilities for survival, treatment efficacies, and complications were extracted from published pediatric studies (Table 1). When more than one study was available for a particular clinical probability, the study with the largest sample size was used for the base case estimate. Utilities for various health states were estimated by a physician with experience in treating patients with sickle cell disease (JSH), based on values used in a published decision analysis comparing stem cell transplant to chronic transfusion in SCD patients with abnormal transcranial Dopplers [8]. Our utility estimates for SCD (0.7 for untreated severe SCD) were also comparable to those reported for more common chronic conditions in the Health and Activity Limitation Index (HALex), such as diabetes (mean HALex=0.62) and congenital heart disease (mean HALex=0.68) [10]. As death from iron overload due to heart dysfunction from myocardium

iron accumulation is extremely low in SCD, particularly in our brief five-year time period, mortality attributed to blood transfusions was estimated based on mortality rates from transfusion-associated lung injury [11, 12]. No deaths attributed to hydroxyurea therapy have been found in the literature in the pediatric population, and an adult study of long-term use of hydroxyurea did not find hydroxyurea toxicity as the cause of death in a cohort of 152 treated adults [13, 14].

Choosing the preferred course of action (model analysis)

Decision trees are analyzed from right to left using a process called rolling back. In this model, each chance node was assigned a value equal to the sum of the utility for each branch weighted by their respective probabilities. The strategy associated with the highest utility was defined as the preferred course of action.

Sensitivity analysis is an important tool for handling the uncertainty inherent in any decision analysis model and evaluates the effect of alternative assumptions on the final result. If changing a variable over a reasonable range of values changes the preferred strategy, the model is considered sensitive to that variable. We performed one-way sensitivity analysis, in which each model input is varied one at a time, for all probabilities and utilities in the model (Table 1). All probabilities from published pediatric studies, or in a few cases adult studies, were used as plausible ranges in sensitivity analysis for clinical probabilities. Finally, we performed an additional sensitivity analysis in which we varied probabilities widely to identify any threshold values at which the preferred strategy changed. Due to the uncertainty in utility estimates, each estimate was widely ranged between +0.2 and -0.2 the baseline utility.

RESULTS

Analysis, or rolling back, of our decision tree revealed that the treatment strategy associated with the highest average utility (quality of life) over a five-year period was stem cell transplant (0.85) (Figure 2). Average utilities for no treatment, chronic transfusion, and hydroxyurea were 0.68, 0.71, and 0.80 respectively. (To put these numbers into perspective, recall that utilities range from 0 (death) to 1 (perfect health).)

One-way sensitivity analysis of clinical parameters over plausible ranges based on variation seen in the published literature revealed that stem cell transplant was the preferred strategy in the large majority of scenarios. One exception was that if the estimated utility of a patient status-post SCT was <0.89, then HU would be preferred over SCT (Table 2). When varying probability estimates over ranges beyond our original sensitivity analysis, we identified additional scenarios in which hydroxyurea would be preferred over stem cell transplant; for example, if the mortality of SCT is >11%, or the probability of graft failure is >23%.

We found that our model was more sensitive to variation in quality of life measurements than the probability of clinical complications. When varying utility estimates, we found that our model was quite sensitive to the quality of life experienced by children on hydroxyurea therapy (both those who continue to have severe disease and those who respond well to HU)

and the quality of life experienced by children who undergo SCT not complicated by graft failure or chronic GVHD.

DISCUSSION

This appears to be the first time decision analysis has been used to compare treatment strategies in children with clinically severe SCD. We found that stem cell transplant was associated with the highest average quality of life, followed by hydroxyurea and chronic transfusions. Unfortunately, all of the data available regarding SCD and stem cell transplant are based on SCT performed using HLA-matched sibling donors, and <10% of patients with SCD have a matched sibling. Even in patients with matched siblings, however, recommending stem cell transplant over hydroxyurea remains a difficult decision for clinicians as transplant is associated with its own morbidity and low, but not negligible, mortality. The results of our model demonstrate that quality of life is also an important factor to consider in this decision.

Our decision analysis model has several limitations that should be noted. First, our model of SCD only follows patients for five years, and is simplistic given the heterogeneity and complexity of this patient population. Even the definition of “severe sickle cell disease” remains a hotly debated point within the field. Our definition was based on definitions used in the clinical trials we extracted data from. However, this definition does not include patients with stroke or those with repetitive pain episodes which are managed at home but have substantial negative impacts on quality of life. The probability of adherence to therapy and the effects of poor adherence on health outcomes were also not considered. We view this model as a “place to start” in the consideration of the impact of clinical probabilities and quality of life in therapeutic decision making for patients with severe SCD. As more data accumulates on the use of hydroxyurea and stem cell transplant in sickle cell disease, and in particular data on the long term outcome of these patients, we hope that future models will be able to handle additional complexity and a longer time frame. As there are few published pediatrics studies, our clinical probability estimates were dependant on small cohorts with limited follow-up periods. Larger studies with much longer longitudinal follow up would allow for more accurate mortality rates. For example, we found that if the mortality of stem cell transplant is 11%, then transplant is no longer the preferred strategy, a number that is not much higher than published estimates.

Due to the absence of direct reports of quality of life from patients with SCD, the most important limitation of our study is that health state utilities were estimated by a physician, with input from a previously published decision analysis and the Health and Activity Limitation Index. However, this previously published model comparing stem cell transplant to chronic transfusion in SCD patients with abnormal transcranial Doppler was similarly limited [8]. Ideally, utilities should be measured directly from patients experiencing the health state in question, which can be done in several different ways. An investigator can measure utilities directly by performing a choice-based valuation technique such as the standard gamble or time trade-off [15]. However, these are time consuming and complex tasks. They are particularly challenging in pediatric research because they require a lengthy attention span and a minimum sixth-grade reading level [16].

The sensitivity of our model to utility estimates, however, demonstrates the necessity of eliciting quality of life data from children with SCD who undergo stem cell transplant or hydroxyurea therapy. An alternative, and more feasible, method of directly measuring utilities would be to use a pre-scored multiattribute health status classification system, such as the Health Utilities Index or the EuroQol-5D [6]. Formulas have been developed to calculate utilities using patient responses to these generic quality-of-life instruments, which are easier and faster to administer and require less advanced reading levels. Panepinto et al recently showed the feasibility of directly measuring utilities by demonstrating that the Pediatric Quality of Life Inventory generic core scales (PedsQL) is a feasible, reliable, and valid tool to measure health-related quality of life in children with sickle cell disease, and that the parent proxy-report differentiates well between children with mild and severe disease [17].

In summary, we performed an initial decision analysis model to identify variables of interest when comparing four clinical strategies for severe sickle cell disease - no treatment, hydroxyurea therapy, chronic transfusions, and stem cell transplantation. Our model reveals that a true comparison of hydroxyurea and stem cell transplant, the two most attractive strategies, cannot occur until investigators directly measure the health-related quality of life in sickle cell patients after stem cell transplant and during hydroxyurea therapy.

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FIGURE ONE.

A schematic representation of the decision analysis model. The square node on the left represents the decision to choose one of four possible treatment strategies. Circular nodes represent chance events, such as the five-year probability of iron overload, graft failure, or death. Triangular nodes at the end of each path in the tree represent the health state utility (quality of life) associated with the full sequence of events in that particular path.

FIGURE TWO.

The decision analysis model after rollback analysis. The stem cell transplant strategy has the highest quality of life, which an average utility of 0.85. Numbers under each branch of the tree represent the probability estimate used in the base case analysis. For example, the mortality of stem cell transplant was estimated to be 6%.

TABLE 1
Estimates for Clinical Probabilities and Quality of Life Measures

For clinical probabilities, base case estimates were extracted from published pediatric studies with the largest sample size. The range of estimates was based on all identified studies in the pediatric literature, or from adult literature if pediatric-specific data were not available. For utility estimates, the range is the base case estimate ± 0.2 .

	Base case estimate	Range	References or sources
CLINICAL PARAMETERS			
Probability of severe SCD			
Hydroxyurea (HU)	27%	20-45%	[2, 18-22]
Chronic transfusion (CTX)	15%	6-15%	[4, 23, 24]
Probability of mortality			
No treatment	3%	1-40%	[25, 26]
Hydroxyurea	0%	0-10%	[14, 27]
Chronic transfusion	1.1%	1-50%	[11]
Stem Cell Transplant (SCT)	6%	1-10%	[3, 28-30]
Probability of iron overload with CTX	95%	0-100%	[31, 32]
Probability of graft failure with SCT	10%	10-18%	[3, 28-30]
Probability of chronic GVHD with SCT	3.8%	7.7-22%	[3, 28-30]
QUALITY OF LIFE MEASURES (UTILITIES)			
Alive, no treatment, severe disease	0.7	0.5-0.9	[8, 10]
Alive, on HU, severe disease	0.65	0.45-0.85	[8, 10]
Alive, on HU, no severe disease	0.85	0.65-1	[8, 10]
Alive, on CTX, severe disease, iron overload	0.55	0.35-0.75	[8, 10]
Alive, on CTX, no severe disease, iron overload	0.75	0.55-0.95	[8, 10]
Alive, on CTX, severe disease, no iron overload	0.60	0.40-0.80	[8, 10]
Alive, on CTX, no severe disease, no iron overload	0.80	0.60-1	[8, 10]
Alive, SCT, graft failure	0.55	0.35-0.75	[8, 10]
Alive, SCT, no graft failure, chronic GVHD	0.65	0.45-0.85	[8, 10]
Alive, SCT, no graft failure, no chronic GVHD	0.95	0.75-1	[8, 10]
Death	0	---	[8, 10]

TABLE 2

Threshold Values Identified in Sensitivity Analysis

We performed one-way sensitivity analysis, in which the value of each clinical probability and quality of life estimate was varied one at a time over a wide range of values. In the majority of cases, estimates had to be varied outside of the plausible range for an intervention other than stem cell transplant to be the preferred strategy.

	Plausible range based on published literature	Results
CLINICAL PARAMETERS		
Probability of severe SCD		
Hydroxyurea (HU)	20-45%	If probability of severe disease <1%, HU preferred over SCT If probability of severe disease >60%, CTX preferred over HU
Chronic transfusion (CTX)	6-15%	If probability of severe disease >43%, no treatment preferred
Probability of mortality		
Hydroxyurea	0-10%	SCT always preferred
Chronic transfusion	1-50%	SCT always preferred
Stem Cell Transplant (SCT)	1-10%	If SCT mortality 11%, HU becomes preferred strategy
Probability of iron overload with CTX	0-100%	SCT always preferred
Probability of graft failure with SCT	10-18%	If probability of graft failure 23%, HU becomes preferred strategy
Probability of chronic GVHD with SCT	7.7-14%	If probability of GVHD 23%, HU becomes preferred strategy
QUALITY OF LIFE MEASURES (UTILITIES)		
Alive, on HU, severe disease	0.45-0.85	If utility >0.843, HU becomes preferred strategy
Alive, on HU, no severe disease	0.65-1	If utility >0.914, HU becomes preferred strategy
Alive, on CTX, severe disease, iron overload	0.35-0.75	SCT always preferred
Alive, on CTX, no severe disease, iron overload	0.55-0.95	SCT always preferred
Alive, on CTX, severe disease, no iron overload	0.40-0.80	SCT always preferred
Alive, on CTX, no severe disease, no iron overload	0.60-1	SCT always preferred
Alive, SCT, graft failure	0.35-0.75	If utility is <0.04, SCT no longer preferred
Alive, SCT, no graft failure, chronic GVHD	0.45-0.85	SCT always preferred
Alive, SCT, no graft failure, no chronic GVHD	0.75-1	If utility is <0.89, HU becomes preferred strategy