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Research paper

Cost-effectiveness of methods in personalized medicine. Results of a decision-analytic model in patients with acute myeloid leukemia with normal karyotype

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ABSTRACT

Background: During the last years, molecular genetic data are increasingly used as prognostic and predictive factors in acute myeloid leukemia (AML). The molecular genetic profile permits a rapid risk categorization and beyond that a prediction of differential treatment efficacy of post-remission chemotherapy versus an allogeneic hematopoietic cell transplantation (HCT) in specific subgroups.
Methods: The aim of this study was to evaluate cost-effectiveness of two different strategies of risk categorization (conventional cytogenetic diagnostics (CCD) versus molecular genetic diagnostics (MGD)) in patients with AML, using a decision-analytic state-transition model. The model is run as (Monte Carlo) microsimulation in which individuals pass through in cycles with a cycle length of one month and a time horizon of ten years.
Findings: Results show that on average, individuals within the MGD group generated about US$ 32,000 higher costs but survived about seven months longer than individuals within the CCD group. This leads to an Incremental Cost-Effectiveness Ratio (ICER) of about US$ 4928 per survived month.
Interpretation: With a GDP (Gross Domestic Product) of US$ 26,467 (€ 33,630) per capita in Germany in 2012, the base-case ICER of US$ 4928 per survived month projected to US$ 59,136 per survived year is in between the simple GDP and the three times GDP per capita.

1. Introduction

Molecular diagnostics of tumor biopsy samples allow a categorization of individual patients into molecular subgroups. The molecular information may be used not only for prognostic purposes but also to provide a more effective, targeted treatment [1]. In the current research, especially in oncological and hematological diseases, this kind of personalized or rather stratified medicine (within this paper the term personalized medicine is used) gains an important role [2,3]. Currently, information about the cost-effectiveness of personalized medicine has remained sparse [4].

Methods of personalized medicine have been increasingly implemented in the diagnosis and selection of therapeutic approaches in patients with acute myeloid leukemia (AML) during the last years. While the common cytogenetic classification has been used for many years to select patients for therapeutic strategies in the consolidation phase, i.e. repetitive cycles of high-dose cytarabine (HiDAC) in patients with “good risk” cytogenetics versus allogeneic hematopoietic cell

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transplantation (HCT) in patients with "high-risk" cytogenetics [5], patients with an "intermediate-risk" karyotype have posed a difficult task of clinical decision-making. Therefore allogeneic HCT was offered, if an HLA (Human Leukocyte Antigen)-identical related (sibling) donor was available, otherwise HiDAC was given and an allogeneic HCT from a matched unrelated donor was postponed until relapse had occurred [6]. With the identification of gene mutations with prognostic impact, the field has changed for AML patients in this intermediate-risk cytogenetic group, in that about 40 percent of these previously "intermediate-risk" patients now are categorized as high-risk and an allogeneic HCT from a related or an unrelated donor is intended in all these patients [7]. In contrast, nearly the same percentage (40 percent) of these patients is categorized as low risk patients who have a very good outcome when they receive the inexpensive consolidation therapy with HiDAC [7]. The selection based on molecular genetic changes, e.g. presence or absence of *FLT3* internal tandem duplication (ITD) in patients with normal karyotype, has not yet been universally adopted [8–11]. However, the genetic profile permits a more refined risk categorization of these patients and therefore a prediction of the efficacy of a specific treatment in a distinct genetic subgroup [12].

While up to now these genetic data are mainly used for prognostic and predictive purposes, there are no studies which have especially looked at the costs-effectiveness of these approaches of personalized medicine including treatment outcome.

The aim of this study was to evaluate the cost-effectiveness of two different strategies for risk categorization (conventional cytogenetic diagnostics (CCD) versus molecular genetic diagnostics (MGD)) and risk-adapted treatment in patients with AML within the German health care context using a decision-analytic state-transition model.

2. Material and methods

2.1. Model design

We developed and validated a Markov state-transition model (manuscript submitted), with a cycle length of one month, for the natural course and treatment of AML for the German health care context. The aim was to evaluate two different strategies according to the categorization of patients into risk categories based either on MGD or on CCD. The model is consistent both with medical knowledge including progress in molecular diagnostics and practical therapies in the treatment of AML in Germany. Medical assumptions according to the structure of the model were validated by medical experts in the field of AML. The disease course of AML was dissected in 13 health states (see Fig. 1).

These states represent either therapy strategies or health conditions of the disease. Transitions between the different states are based on disease progression and all possible medical options. Within the MGD, AML-patients were categorized as low- or high-risk based on their molecular disease profile. This risk categorization was done according to the mutational status in three genes, *FLT3-ITD*, *NPM1,* and *CEBPA* [9]. Regarding the model structure two strategies (CCD and MGD) were compared. The MGD branch was divided into two further branches representing low- and high-risk, while the CCD branch remained undivided (see Fig. 2).

A Monte-Carlo-microsimulation (using seeding) with 1,000,000 runs was performed. A microsimulation was preferred over a cohort model because of the fact that microsimulation enables the use of tracker-variables and therefore the track of each individual's history regarding the disease [13].

2.2. Outcomes

In the analytic time horizon, we evaluated the following clinical and health-economic outcomes: (1) *survived months*, (2) total *costs,* and (3) the *incremental cost-effectiveness ratio (ICER)* in US dollars (US$) per survived month. As recommended, a half cycle-correction was applied [13–16]. In order to convert future costs to their present value, costs and effectiveness values are discounted at 3 percent per year in the base-case analysis [17].

2.3. Model input parameters

2.3.1. Natural history parameters and clinical data

Clinical data and data concerning the natural history of disease were derived from trial data of the German Austrian AML study group (AMLSG) [7]. The population entering the Markov-state transition model comprises adult male and female AML-patients with an age between 16 and 60 years who were eligible for intensive induction chemotherapy. Data for the MGD strategy refers to 511 patients with a median age of 47 years (range 18–60 years; 51·1% male, 48·9% female) and normal karyotype [18]. For the CCD strategy, data of 870 patients with a median age of 46 years (range 16–60 years) and a normal karyotype (46·8% male, 53·2% female) were included into the model [7]. Patients within the CCD group had been enrolled in one of four multicenter prospective trials of AMLSG between July 1993 and November 2004. Patients within the MGD group had been entered into a prospective randomized controlled treatment trial (AMLSG 07-04) between August 2004 and August 2009. Induction therapy consisting of two cycles was followed by consolidation therapy. There was a difference regarding these two patient groups according to the treatment strategy. For patients within the CCD strategy who had achieved a complete remission after induction chemotherapy, allogeneic HCT replaced consolidation chemotherapy only in case of an available HLA-identical sibling donor. In contrast, patients within the MGD group were treated according to their molecular profile as high- or low-risk patients. Data used in the base-case analysis of the Markov-state transition model concerning the distribution of high- to low-risk patients differs in comparison to the statements from the literature (see introduction), but this aspect has been taken into account in the sensitivity analysis. The relation from high- to low-risk patients was 71 percent to 29 percent in the MGD group. Patients with the genotype *FLT3-ITD* (including combinations with *FLT3-ITD*) and triple negative (NPM1-wt, CEBPA-wt, FLT3-ITDneg) were treated as high-risk, which means that after induction therapy allogeneic HCT was intended, including not only related but also unrelated HLA-identical grafts. In contrast, low risk patients were only transplanted in complete remission, if an HLA-identical related (sibling) donor was available. This means that within the CCD strategy, 40 percent of patients were actually transplanted while within the MGD strategy, 66 percent of the patients underwent allogeneic HCT. As a result, 75 percent of high-risk patients and 43 percent of low-risk patients in the MGD group were transplanted.

Transition probabilities in the decision-analytic model, were extracted from clinical data [7,18], or based on expert estimates (N = 1; AG). Where necessary, data were transformed to monthly probabilities in order to use them in the model [19,20].

2.3.2. Effectiveness

In order to compare the survival of patients treated according to their risk categorization, health outcome evaluated, in consideration of the cycle length, was defined as survived months. For adjustment, a HCC was performed. The effectiveness payoff was discounted with a rate of 3 percent in the base-case and with 0 and 5 percent in the sensitivity analysis.

2.3.3. Economic data

Economic data used to populate the model include direct costs of testing (laboratory costs) as well as inpatient and outpatient costs.

Costs of testing consist of costs for CCD or costs for MGD supplementary. For both testing strategies, costs have been requested in *Münchner Leukämie Labor GmbH* and *Institut für Zell- und Molekularpathologie, Medizinische Mochschule Hannover (MHH)*. The

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