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Medical costs of treatment and survival of patients with acute myeloid leukemia in Belgium

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ABSTRACT

The advent of new cell-based immunotherapies for leukemia offers treatment possibilities for certain leukemia subgroups. The wider acceptability of these new technologies in clinical practice will depend on its impact on survival and costs. Due to the small patient groups who have received it, these aspects have remained understudied. This non-randomized single-center study evaluated medical costs and survival for acute myeloid leukemia between 2005 and 2010 in 50 patients: patients treated with induction and consolidation chemotherapy (ICT) alone; patients treated with ICT plus allogeneic hematopoietic stem cell transplantation (HCT), which is the current preferred post-remission therapy in patients with intermediate- and poor-risk AML with few co-morbidities, and patients treated with ICT plus immunotherapy using autologous dendritic cells (DC) engineered to express the Wilms' tumor protein (WT1). Total costs including post-consolidation costs on medical care at the hematology ward and outpatient clinic, pharmaceutical prescriptions, intensive care ward, laboratory tests and medical imaging were analyzed. Survival was markedly better in HCT and DC. HCT and DC were more costly than ICT. The median total costs for HCT and DC were similar. These results need to be confirmed to enable more thorough cost-effectiveness analyses, based on observations from multicenter, randomized clinical trials and preferably using quality-adjusted life-years as an outcome measure.

Keywords

Costs

Acute myeloid leukemia

Post-consolidation treatment

Hematopoietic stem cell transplantation

Dendritic cell vaccination

Wilm's tumor protein

1. Introduction

Acute myeloid leukemia (AML) is the most common form of acute leukemia in adults, particularly in individuals over 60 years of age. The standard initial treatment modality for (AML) is intensive chemotherapy with complete remission (CR) achieved in up to 60% of adults with de novo AML who are younger than 70, while in the older adults CR rates are much lower [1,2]. An important problem facing AML patients is the high relapse rate which has an impact on overall survival (OS) [3-5].

Current consensus, based on cytogenetic risk, recommends allogeneic hematopoietic stem cell transplantation (HCT) for intermediate- and poor-risk AML in first CR [6]. For those patients HCT offers significant relapse-free survival and OS benefits. Substantive advances in the past decade allowed for a wider spectrum of patients to undergo HCT but this procedure is still beset by morbitity and mortality in parts of the patients [7].

Novel immunotherapeutic strategies to avoid or delay relapse in AML are being tested in early clinical studies. Some of the most promising are T-cell engaging antibody constructs, adoptive transfer with chimeric antigen receptor (CAR) T cells and dendritic cell (DC) vaccination [8-14].

AML treatment, which can be given with supportive and/or curative intent, is considered expensive compared with that for other cancers. Studies addressing the economic costs of AML found that the key cost drivers appear to be hospitalization length related to initial chemotherapy, relapse of disease and HCT. However, published cost studies on AML are relatively sparse and they cover only limited inpatient chemotherapy or HCT treatment phases with a maximum follow up of 1 year, mostly excluding costs after relapse and without OS data [15-24].

In this study we measured the full costs of AML treatment and analyzed its cost-effectiveness in relation to OS results.

2. Materials and methods

2.1. Patients

Between January 2005 and December 2010, a total of 50 adults with AML received anti-leukemic therapy as part of current practice at the Antwerp University Hospital and according to international recommendations [25,26]. Fifteen patients were treated with induction and consolidation chemotherapy alone (ICT group), 25 patients with

chemotherapy followed by allogeneic HCT (HCT group, 16 from a HLA-identical sibling donor and 9 from a matched unrelated donor) and 10 patients with chemotherapy followed by immunotherapy using dendritic cells engineered to express the Wilms' tumor protein WT1 (DC group) and enrolled in the NCT00834002 phase I/II trial [13]. Patients aged ≥75 years or with a WHO performance status ≥2 were not eligible for HCT. If they were at high risk for relapse (poor risk cytogenetic or molecular markers, hyperleukocytosis at presentation and/or second remission) and there was no sibling allotransplant donor available, they were included in the DC trial. The Ethics Committee approved this cost study and patients provided informed consent for HCT or for enrollment in the DC study. Data regarding patient characteristics and costs attributable to AML were obtained from patients' medical records from diagnosis until death or last day of registration (November 2014) with a median follow up of 7 years (range 4-10 years) (Table 1).

2.2. Treatment

The choice of treatment depended on the patient's risk of relapse, performance status and the availability of an HLA-identical donor. Induction chemotherapy consisted of idarubicin in combination with cytarabine. A salvage course of high dose cytarabine and mitoxantrone was administered to patients with persistent leukemia. In the absence of contra-indications to further intensive chemotherapy, patients in CR were eligible for consolidation chemotherapy. Conditioning for myeloablative HCT was with high-dose cyclophosphamide and fractionated 12 Gy (6 x 2 Gy) total body irradiation with or without antithymocyte globulin. Conditioning for non-myeloablative HCT was with fludarabin and busulphan. Graft-versus-host disease prophylaxis included cyclosporine A, methotrexate, antithymocyte globulin and/or mycophenolate mofetil. Stem cell source was either bone marrow or granulocyte colony-stimulating factor-mobilized peripheral blood stem cells. The assignment of conditioning regimen, graft-versus-host disease prophylaxis and/or graft source was based on protocols or clinical decisions. Blood was obtained weekly after engraftment for cytomegalovirus testing and patients were treated pre-emptively with ganciclovir or valganciclovir if clinically indicated. Patients with neutropenic fever were treated with broad-spectrum antibiotics and with antifungal agents, if needed. For hemoglobin levels below 9 g/dl, two units of packed cells were administered and for a platelet count below 20 x 10^9/l one thrombocyte concentrate. Patients were hospitalized to receive remission induction, consolidation and pre-HCT conditioning regimen and remained hospitalized until neutrophil engraftment, adequate oral intake and absence of uncontrolled medical problems.

DC were prepared as described elsewhere [12,13]. Intradermal administration of DC was done 4 times with a two-week interval, followed by 2-monthly vaccinations.

2.3. Cost calculation

Inpatient and outpatients costs of treatment for AML were obtained from the accounting system of the hospital. Information on medical resource use was collected from electronic medical records. Professional and facility charges were collected using electronic billing information. Drug costs and drug administration costs were based on list prices published by the Belgian National Institute for Health and Disability Insurance. For the purpose of the current analysis, inpatient and outpatient costs including care at the hematology ward, pharmaceutical products, intensive care unit, laboratory tests and medical imaging were analyzed. At the time of the study, the cost of DC vaccine preparation was € 20,450 per patient.

Statistical analysis

The effects in terms of longevity were expressed as number of days of OS, as well as the proportion of OS relative to background life expectancy by age and gender. The patients' gender and age at diagnosis were available, and coinciding overall age and gender-specific life expectancy in Belgium was obtained from the national official registry (reference: FOD Economie, Algemene Directie Statistiek en Economische Informatie; http://statbel.fgov.be). Descriptive analyses of costs and OS within groups were followed by comparative analyses between the three groups. The incremental cost-effectiveness ratios of one group versus another group were expressed in terms of direct hospital costs per life-year gained. We bootstrapped (10,000 iterations using Latin Hypercube sampling with replacement) cost and effect pairs from each of the three groups to explore uncertainty around our estimates, in view of the small group sizes. Bootstrapping is a standard nonparametric approach to explore uncertainty intervals of skewed data, especially when data points are limited [27]. The 10,000 comparative cost and effect pairs were used to specify 95% percentiles around the median. To further illustrate the uncertainty in the comparative cost-effectiveness between the groups, cost-effectiveness acceptability curves were constructed.

3. Results

Median OS and costs are shown in Table 1. Survival was better in the HCT and DC groups (339 and 477 versus 57 days in the ICT group). Only 2 patients in the IC group lived long enough to receive consolidation therapy. Median induction/consolidation costs were around € 32,000 in the ICT group and € 80,000 in the HCT group. Median post-consolidation costs were € 35,000 without HCT in the ICT group and € 117,000 with HCT. Those costs are comparable to those recently published in The Netherlands for a maximum follow-up of 1 year [15]. The total costs of AML treatment were similar in the HCT and DC groups (€ 134,000 and € 109,000) and higher than in the ICT group (€ 32,000). The proportion of post-consolidation costs to total costs for the HCT and DC groups was 64% and 53%, respectively.

Incremental between-group analyses, by comparing individuals belonging to different groups using bootstrapping showed that both HCT and DC are more costly than ICT. HCT and DC were more effective than ICT for the majority of patients. In HCT and DC, improved OS over ICT was robust, with probabilities exceeding 90% of the bootstrap comparisons. DC showed improved OS over HCT, with high probabilities of 79% for unadjusted and even of 89% for survival adjusted relative to life expectancy (Table 2).

In the cost-effectiveness plane showing the distribution of joint costs and effects for a representative sample of the 10,000 bootstrapped comparisons between the DC and HCT groups (Fig 1), we found a 2% probability for DC to be more costly and less effective than HCT (North West quadrant), a 9% probability for DC to be less costly and less effective than HCT (South West quadrant), a 21% probability for DC to be more costly and more effective than HCT (North East quadrant) and a 67% probability for DC to be less costly and more effective than HCT (South East quadrant). If we only consider survival after diagnosis up to the present time and ignore quality of life impacts and non-hospital costs, then, for instance at a willingness to pay of € 40,000 per life year gained [28], there is 75% probability of making a cost-effective choice if DC is chosen over HCT (Fig 2). In Belgium, there is no explicit societal willingness to pay, but amounts between € 30,000 and € 50,000 per Quality-Adjusted Life-Year (QALY) gained are often cited as benchmark.

4. Discussion

It is critical to focus on developing new therapies that prevent relapse and maintain AML patients' CR status to maximize survival. In addition to the fact that this is important from the medical point of view, it also has a justification from the economic perspective. The

major strengths of the present study is that it evaluated not only direct inpatient medical costs but also outpatient and rehospitalization costs both of HCT and of DC-based immunotherapy and it has a long follow up and survival data. Future research priority is that these results need to be updated for cost-effectiveness analysis with QALYs as an outcome measure in a multicenter, randomized clinical trial of post-remission strategies in patients with AML.

Authorship: All authors have made substantial contributions to the conception and design of the study, acquisition of data, and analysis and interpretation of data. ALVDV, PB and ZB were involved in writing the manuscript, revising it critically for content and final approval of the manuscript to be submitted.

Conflicts of interest

The authors have no conflicts of interest to disclose.

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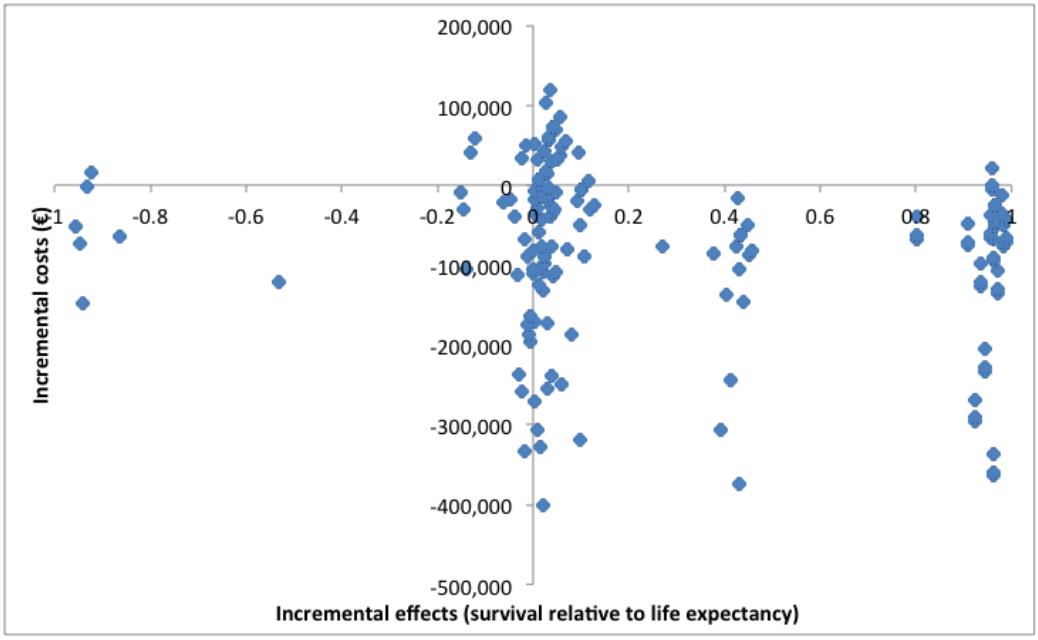
Fig 1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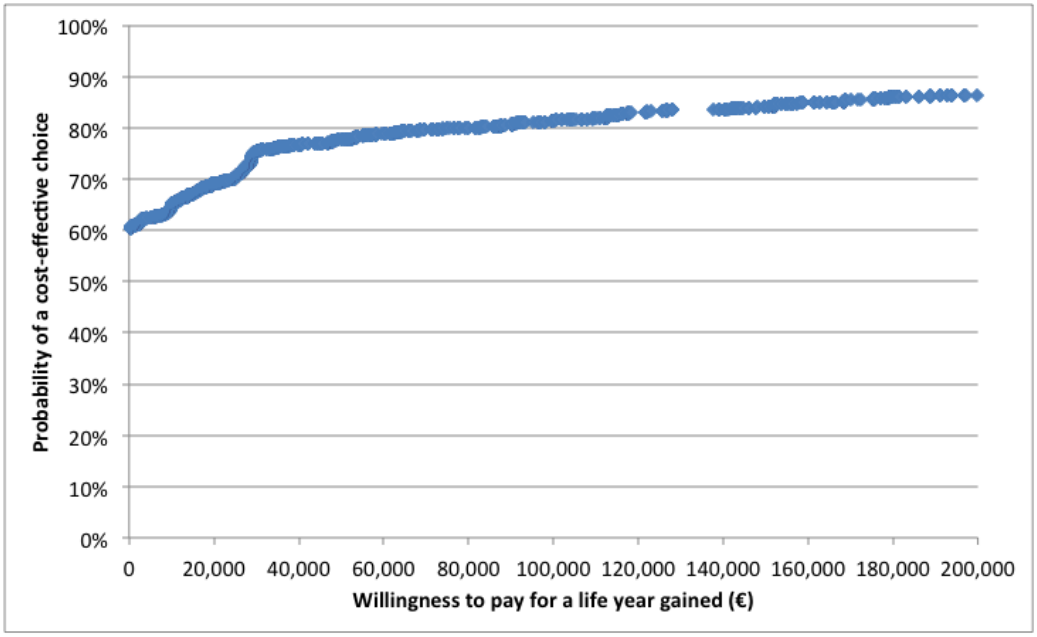
Incremental costs (€)
Incremental effects (survival relative to life expectancy)

Fig 2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Probability of a cost-effective choice
Willingness to pay for a life year gained (€)

Figure legends

Fig 1: Cost-effectiveness plane showing the distribution of joint costs (vertical axis) and survival related to life expectancy effects (horizontal axis) for a representative sample of the 10,000 bootstrapped comparisons between the DC and HCT groups (HCT is the comparator, plotted in the origin of the plane).

Fig 2: Cost-effectiveness acceptability curve of DC versus HCT groups.

Table 1: Patient characteristics in the three groups

	ICT group (n=15)	HCT group (n=25)	DC group (n=10)
Median age (years)	78 (range 41-89)	51 (range 15-73)	61 (range 33-78)
Median OS (days)	57 (range 2-1771)	339 (range 180-1659)	477 (range 219-3116)
Median OS relative to LE (%)	1.2 (range 0-40.9)	3.4 (range 1.6-19.8)	7.7 (range 4.5-100.0)
Median total costs (€)	32,649 (range 4,760-140,383)	134,112 (range 122,325-378,117)	109,856 (range 45,114-207,732)
Median ind/cons costs (€)	32,649 (range 4,759-140,383)	80,093 (range 41,776-365,749)	57,623 (range 12,516-93,788)
Median post-cons costs (€)	35,581 (range 30,069-41,093)	117,241 (range 31,364-304,366)	40,749 (range 26,908-156,870)

OS: overall survival; ind: induction; cons: consolidation; LE: life expectancy

Table 2: Incremental analyses between the three groups

	HCT group versus ICT group	DC group versus ICT group	DC group versus HCT group
Median OS (days)	282 (range -1350 to1636)	459 (range -720 to 3059)	933 (range -785 to 2973)
Median OS relative to LE (%)	0.0225 (range -0.3532 to 0.1955)	0.0749 (range -0.1245 to 0.9981)	0.0488 (range -0.0619 to 0.9657)
Median total costs (€)	112,452 (range 7,096 to 352,679)	69,382 (range -39,681 to 182,294)	-46,777 (range -270,563 to 73,620)

OS: overall survival; LE: life expectancy