Physician uncertainty aversion impacts medical decision making for older patients with acute myeloid leukemia: results of a national survey

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ABSTRACT

Elderly patients with acute myeloid leukemia can be treated with intensive chemotherapy, low-intensity therapy such as low-dose aracytine or hypomethylating agents, or best supportive care. The choice between these treatments is a function of many patient-related and disease-related factors. We investigated how physicians' behavioral characteristics affect medical decision-making between intensive and non-intensive therapy in this setting. A nationwide cross-sectional online survey of hematologists collected data on medical decision-making for 6 clinical vignettes involving older acute myeloid leukemia patients that were representative of routine practice. Questionnaires elicited physicians' demographic and occupational characteristics along with their individual behavioral characteristics according to a decision theory framework. From the pattern of responses to the vignettes, a K-means clustering algorithm was used to distinguish those who were likely to prescribe more intensive therapy and those who were likely to prescribe less intensive or no therapy. Multivariate analyses were used to identify physician's characteristics predictive of medical decision-making. We obtained 230 assessable answers, which represented an adjusted response rate of 45.4%. A multivariate model (n=210) revealed that physicians averse to uncertainty recommend significantly more intensive chemotherapy: Odds Ratio (OR) [95% Confidence Interval (CI)]: 1.15 [1.01;1.30]; *P*=0.039. Male physicians who do not conform to the expected utility model (assumed as economically irrational) recommend more intensive chemotherapy [OR (95% CI) = 3.45 (1.34; 8.85); *P*=0.01]. Patient volume per physician also correlated with therapy intensity [OR (95% CI)=0.98 (0.96; 0.99); *P*=0.032]. The physicians' medical decision-making was not affected by their age, years of experience, or hospital facility. The significant association between medical decision and individual behavioral characteristics of the physician identifies a novel non-biological factor that may affect acute myeloid leukemia patients' outcomes and explain variations in clinical practice. It should also encourage the use of validated predictive models and the description of novel biomarkers to best select patients for intensive chemotherapy or low-intensity therapy.

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Introduction

Outside clinical trials, therapy options offered to elderly acute myeloid leukemia (AML) patients are limited.[1,2] They can be summarized as intensive chemotherapy (IC), low-intensity therapy (LIT) or best supportive care (BSC) depending on patient-specific[3] and AML-related[4] prognostic factors. Although scoring systems have been proposed to rationalize the medical decision-making (MDM) between intensive and non-intensive approaches,[5,6] large variations in clinical practice remain,[7] which underlines the paucity of evidence supporting medical decisions. International guidelines define available intensive or low-intensity options, but in most cases they give the physician the responsibility of determining which option should be recommended for a particular patient. The AZA-AML-001[8] and DACO 16[9] phase III studies failed to demonstrate the superiority of hypomethylating agents (azacitidine and decitabine, respectively) over conventional chemotherapy for patients over 65 years of age with non-proliferative AML, which increases the uncertainty regarding the optimum strategy for any individual patient. In the AZA-AML-001 trial, only 18% of patients were allocated to AZA *versus* IC as compared to 82% to AZA *versus* low-dose aracytine (LDAC) or BSC, suggesting that physicians' decisions were already biased toward LIT. In addition, when physician-investigators in the UK National Cancer Research Institute's AML-14 trial[10,11] were offered the possibility of an optional randomization between intensive and non-intensive therapy, they preferred to bypass this randomization and allocate their patients directly into the intensive or non-intensive arms. Multivariate comparison of the characteristics of the patients treated intensively or non-intensively in this AML trial revealed that the physician was a strong determinant of the choice, which clearly demonstrates a physician effect in this setting. Previous studies have investigated the impact of physician's professional characteristics on their decision-making for hematologic malignancies, particularly in the setting of allogeneic stem cell transplantation,[12,13] but these studies mostly focused on age, specialty, and hospital facility. Much less attention has been given to an individual physician's non-professional characteristics.

Uncertainty is a crucial, multifaceted component of the therapeutic decision for older patients with AML.[14] Intensive chemotherapy offers the greatest chance of complete remission (CR) but is associated with a significant risk of early death (ED), while hypomethylating agents yield a lower chance of CR but lower risk of ED. Thus, for physicians treating an older AML patient, uncertainty is a pre-condition for the decision itself, which underscores the need to investigate how physicians deal with it.[15,16]

In behavioral economics and decision sciences, attitudes towards risk and uncertainty are crucial psychological traits that may explain medical choices and practices.[17,18] They aim to describe individual decisions in situations where choices have uncertain consequences. Risk- or uncertainty-averse individuals prefer a safer option (with greater chances of a smaller gain) than risk- or uncertainty-seeking individuals who will choose a riskier option (with lower chances of a larger gain). The difference between risk and uncertainty is that, for an uncertain option, the probability of success (or gain) is unknown. In economics, the gold standard of rationality is the expected utility model[19] (EU) although much experimental evidence in behavioral sciences shows departures from EU.[20] The Allais paradoxes[21,22] are decision tasks used to classify individuals as conforming to EU or not (non-EU). The most popular non-EU model is prospect theory.[23] Investigating the association between practice variations in AML therapy and physician's behavioral characteristics (such as risk or uncertainty aversion) and types (EU *vs.* non–EU) may help define new determinants of these variations and to propose corrective measures to improve the quality of care.[24,25] We hypothesized that individual physicians' attitudes towards risk and uncertainty have an impact on their decision-making process for elderly patients with AML.

Methods

Survey design

We conducted a national cross-sectional online survey of French hematologists to evaluate the impact of demographic, occupational and behavioral characteristics on medical decision-making for selected clinical cases of older patients with AML presented as clinical vignettes. As compared with other tools such as chart abstraction or standardized patients, clinical vignettes have been validated as a simple case-mix adjusted method for measuring quality of care and practice variations.[26] All the hematologist-oncologists practising in France who provide direct patient care for adults with AML were eligible. A first draft of the questionnaire was developed and subsequently modified after pilot testing with 20 hematologists. Overall, the survey contained 27 questions and took 10-15 minutes to complete. The questionnaire is available in *Online Supplementary Appendix Section I.*

Survey instrument

Physician's demographic and occupational characteristics included age, gender, medical specialty, subspecialty, hospital facility, hierarchical position, year of graduation, patient volume (number of AML patients aged 60 years or older each physician treated annually), and self-evaluation of expertise in the field of AML.

Four hypothetical AML patients aged 60 years or older were selected as representative of clinical practice and were summarized by 3 local specialists (PB, SB and CR) as Vignettes #1 to #4 (Table 1). Each of these cases highlighted distinct and difficult representative situations regarding their age, comorbidity, family environment or AML biology. Vignettes #5 and #6 were similar to Vignette #4 but included a unique variation related to age (increased from 63 to 73-years old in Vignette #5) or white blood cell (WBC) count (increased from 2.5 to 40 x10^9/L in Vignette #6). For each of these 6 vignettes, the close-ended treatment options were: 1) intensive chemotherapy; 2) low-intensity therapy; or 3) best supportive care.

To measure physicians' attitudes towards risk and uncertainty, we used four different elicitation methods (Figure 1) that have been validated in representative national surveys.[27] The first two measures are certainty equivalent elicitation and the third one consisted of two binary lottery choices. These tasks involve risky choices with financial consequences. The fourth method is a Likert scale that measures willingness to take risks in four different domains (*Online Supplementary Appendix Section II*).

Survey implementation

The Ethics committee of the French Society of Hematology approved the study and provided an incentive email accompanying the online survey invitation. Physicians identified from the French

Table 1. Clinical Vignettes of older AML patients derived from real life activity.

General instructions
• Six clinical cases of AML patients derived from real life activity are presented.
• **You are not alone to decide but we are asking you to state which treatment option would you recommend for each of these patients among:**
1. Intensive chemotherapy
2. Low-intensity therapy (hypomethylating agent or low-dose cytarabine)
3. Best supportive care
• These patients have announced they would accept medical treatment decision
• You do not have any clinical trial to offer them.
• You have unlimited possibilities of hospitalization as inpatient or outpatient
Vignette#1: A 72-year old female, with no comorbidity. Normal cardiac function. Untreated low-risk myelodysplastic syndrome for 3 years (refractory anemia, IPSS 0.5). CBC: WBC 1x10^9/L incl. neutrophil count 0.3x10^9/L and PB count 5%, Hb 11g/dL, platelets 120x10^9/L. BMA: FAB1 AML with 40% marrow blast infiltrate, and adverse karyotype (monosomy 7).
Vignette#2: A 75-year old male, coronary artery disease with anterior interventricular artery stenting in 2010, controlled ischemic cardiopathy with medication (LVEF 52%), ECOG 2, recent weight loss 4 kg. CBC: WBC count 75x10^9/L, PB blast count 40%, Hb 10 g/dL, platelets 50x10^9/L. BMA: FAB2 AML (marrow blast infiltrate 60%) with normal karyotype**.**
Vignette#3: A 77-year old female, with an 8-year history of hypertension controlled with angiotensin-converting-enzyme inhibitor, a recent echocardiogram showed LVEF of 55%. She is natural carer of her husband affected by Alzheimer's disease. CBC: WBC 18x10^9/L incl. 25% peripheral blast, Hb 10g/dL, platelets 80x10^9/L, BMA: FAB4 AML with favorable karyotype (inv16).
Vignette#4: A 63-year old male, with a 5-year history of asymptomatic Parkinson disease and recently diagnosed with an asymptomatic carotid artery stenosis (90%). CBC: WBC 2x10^9/L incl. 5% PB blast count, Hb 8g/dL, platelets 35x10^9/L. BMA: FAB2 AML (marrow blast infiltrate 30%, tri-lineage dysplasia) with complex Karyotype incl. inv3, -5q, -7.
Vignette#5: Patient from the Vignette#4 but **73-year old.**
Vignette#6: Patient from the Vignette#4 but **with WBC count 40x10^9/L incl. PB blast count 25%.**

IPSS: International Prognosis Scoring System; CBC: complete blood count; WBC: white blood cell count; Hb: hemoglobin; FAB: French-American-British classification system; BMA: bone marrow aspirate; PB peripheral blast; LVEF: left ventricular ejection fraction; ECOG: Eastern Cooperative Oncology Group Performance Status.

Society of Hematology mailing list received a unique link to enter the survey or opt out. After duplicate names were removed, the panel of potentially eligible subjects contained 1337 physicians, including 220 residents with an email address. On November 30th 2015 we emailed the survey link; non-responders received three subsequent reminders every eight weeks. Before entering the survey, physicians were informed they would not be compensated for their participation. Consent was implied based on reading the survey goals and participating. Assessable respondents included those who answered the 6 vignettes. Data were collected from November 30th 2015 to June 6th 2016, and analyzed at the Toulouse University Cancer Institute and Toulouse Faculty of Medicine.

Statistical analysis

We described physicians' characteristics using counts and frequency for qualitative data, and mean and standard deviation for quantitative data.

To assess the clinician pattern of decision-making for the 6 clinical vignettes, we used K-means clustering to define clinician groups with homogeneous patterns of responses to the clinical cases.[28] The aim of this method was to define clusters of subjects by maximizing the between-cluster differences in the subjects' medical choices and by minimizing the within-cluster differences in subjects' medical choices. This allowed us to define two clusters: clinicians more likely to choose intensive chemotherapy (IC), i.e. the "intensive treatment group" (IC group), and those who were more likely to choose less intensive therapy, i.e. the "non-intensive treatment group" (Non-IC group). Only the K-means analyses are presented in this paper. A 6-18 point MDM-score was also calculated for each physician, assigning 1 point for IC, 2 points for LIT, and 3 points for BSC from the responses in the 6 vignettes. The results of this score and its association with the K-means clustering are given in *Online Supplementary Table S1*. We first tested the physicians' demographic, occupational and behavioral characteristics associated with belonging to the IC group in bivariate analyses at the threshold of 0.2. These variables were then included in a multivariate model systematically adjusted for age and gender. From this step, the variables to keep in the final parsimonious model were determined using a stepwise backward selection based on log-likelihood tests between nested models. All analyses were made using STATA release 14 (Stata Corp LP, College Station, TX, USA).

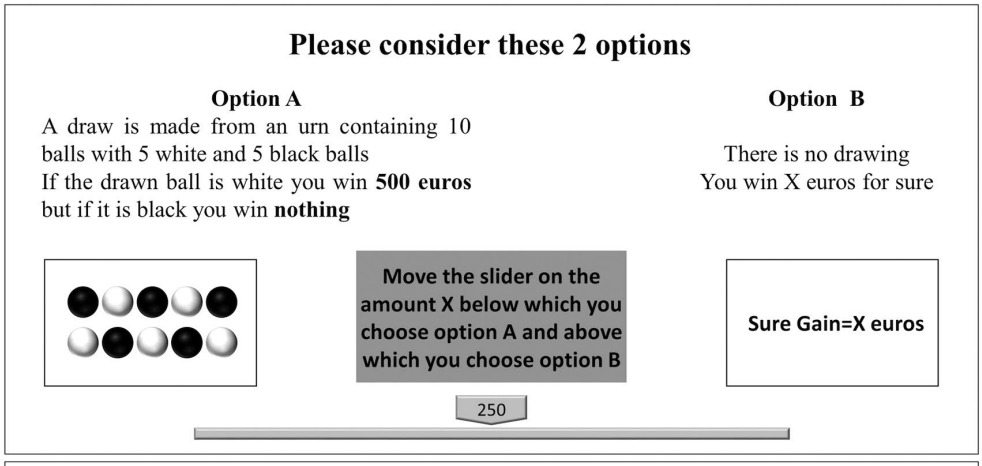
Results

Of the 1337 invitations sent out to complete the questionnaire, 1295 were eligible and 230 completed questionnaires were received (response rate: 17.20%). According to the American Association of Public Opinion Reporting standard definitions, and by taking the characteristics of the mailing list and the interrogated population into account, the adjusted response rate was 45.4% (see *Online Supplementary Table S2*). No differences were found according to gender or by geographical area between respondents and non-respondents (see *Online Supplementary Table S3*).

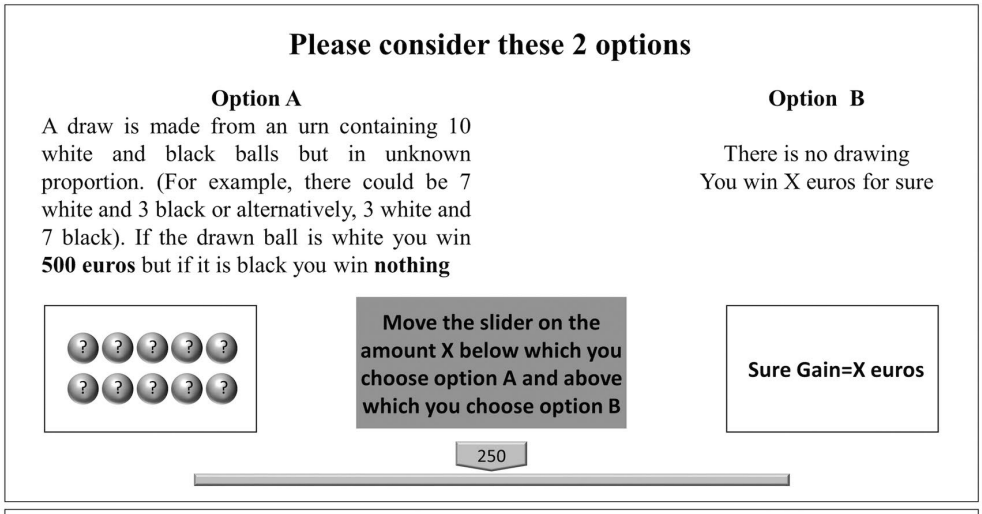
Respondents' demographic and occupational characteristics

The median age of the respondent cohort was 42 years [standard deviation (SD)±11.2], 123 were male (54%), 160

A



B



C

In the next two questions we are asking you to make choices between two options. There is no wrong answer. You just have to choose as if you were really facing this choice tasks

- **Choice 1 Which option do you prefer?**
  Option A gives you 100% chance to win 2000 euros
  Option B gives you 80% chance to win 3000 euros and 20% chance to win 0 euro
- **Choice 2 Which option do you prefer?**
  Option C gives you 25% chance to win 2000 euros and 75% chance to win 0 euro
  Option D gives you 20% chance to win 3000 euros and 80% chance to win 0 euro

D

In this question you have to self-estimate your willingness to take risk in different domains:
(0 being "not at all willing to take risk" and 10 "fully-prepared to take risk")

In your daily life:	□0 □1 □2 □3 □4 □5 □6 □7 □8 □9 □10
For four personal finances:	□0 □1 □2 □3 □4 □5 □6 □7 □8 □9 □10
For your patients' health:	□0 □1 □2 □3 □4 □5 □6 □7 □8 □9 □10
For your own health:	□0 □1 □2 □3 □4 □5 □6 □7 □8 □9 □10

Figure 1. Behavioral tasks. (A) Physician's individual risk aversion evaluation. The closer the scroll bar is to 500 euros, the more risk-seeking the behavior; the lower the score bar, the greater the aversion to risk. E.g. if the scroll bar is at 200 euros, the person prefers a 50% chance of winning 500 euros to a 100% chance of winning 190 euros. If the scroll bar is at 300 Euros, the person prefers a 50% chance of winning 500 euros to a 100% chance of winning 290 euros. The latter is riskier since you are giving up more certain money (290 *vs.* 190) for a chance to win the same amount (500 euros). (B) Physician's individual uncertainty aversion evaluation. The same line of reasoning applies to the uncertainty aversion evaluation except that for option A, the probability of gain is unknown. The closer the scroll bar is to 500 euros the more uncertainty-seeking the behavior; the lower the scroll bar, the greater the aversion to uncertainty. (C) Classic binary choices from Kahneman and Tversky. Choice patterns AC and BD conform to the expected utility theory. Choice patterns AD and BC do not conform to expected utility theory (for further details see *Online Supplementary Appendix, Section 2*). (D) Self-evaluation of the willingness to take risk in four different domains.

were attending physicians or professors (70%), 166 worked in an academic center (72%), 197 were specialized in hematology (86%), and the mean patient volume per physician was 20.7 (SD±17.1).

Medical decision-making among clinical vignettes

The physicians' decisions about the 6 clinical vignettes assessing front-line therapy for older AML patient are summarized in Figure 2. The most controversial case was Vignette #4 for which 50.8% of respondents recommended IC *versus* 49.2% opting for a non-intensive approach. Increasing the age of this patient in Vignette #5 resulted in a marked decrease (from 50.8% to 6.9%) in the proportion of respondents choosing IC. Alternatively, increasing the WBC in Vignette #6 increased the proportion of physicians who recommended an IC from 50.8% to 64.7%. These practice variations induced by modifying classical AML prognosis factors were expected, and they thus provide internal quality control of non-random responses to the online survey (internal coherence criteria).

Aversion towards risk and uncertainty

The mean certainty equivalent under risk was 277 euros (SD±130). This was significantly different from the expected value of the lottery (250 euros), revealing global risk-seeking among our sample (unpaired *t*-test, *P*=0.03). Under uncertainty conditions, the mean certainty equivalent was 241 euros (SD±136). This was significantly lower than under risk (paired *t*-test, *P*<0.001) and reveals an overall ambiguity aversion among our sample. More specifically, of the 212 respondents, 110 are ambiguity averse, 52

Table 2. Panel Description (n=230), and Bivariate Comparison of the Physicians from IC and non-IC Groups.

	Overall sample		Non-IC group		IC group		Global *P*-value of the bivariate analysis of the characteristics related with belonging to IC group[a]
	n	%	n	%	n	%	
Demographical characteristics							
Gender							
Men	123	53	31	*44*	92	*57*	*0.064*
Women	107	47	39	*56*	68	*43*	
Age (n=230) (mean± SD)	42.0 ±11.2		42.3 ±11.1		41.8 ±11.3		*0.792*
Occupational characteristics							
Clinical speciality							
Other than hematology	64	*28*	18	*26*	46	*29*	*0.636*
Hematology	166	*72*	52	*74*	114	*71*	
Workplace							
Non-academic centers	64	*28*	18	*26*	46	*29*	*0.636*
Academic centers	166	*72*	52	*74*	114	*71*	
Region							
North	34	*15*	6	*9*	28	*18*	*0.227*
East	38	*17*	8	*11*	30	*19*	
West	30	*13*	11	*16*	19	*12*	
South-west	45	*20*	13	*19*	32	*20*	
South Méditerranée	27	*12*	9	*13*	18	*11*	
Rhone-Alpes/Auvergne	24	*10*	9	*13*	15	*9*	
Ile de France	32	*14*	14	*20*	18	*11*	
Status							
Few or no decision-making role	70	*30*	23	*33*	47	*29*	*0.597*
Decision-making role	160	*70*	47	*67*	113	*71*	
Occupational experience (n=210) (means ± SD)	16.9±10.9		17.3±10.8		16.8±11		*0.772*
Activity in AML pts aged > 60 / year (n=210) (means ± SD)	20.7±17.1		24.5±18.5		19.1±16.2		*0.034*
Behavioral characteristics							
Attitude towards uncertainty (n=213) (means ± SD)	242±136		276±149		228±127		*0.031*[b]
Attitude towards risks (n=212) (means ± SD)	277±130		296±150		269±120		*0.131*[b]
Expected utility							
yes (n=101)	101	*48*	36	*57*	65	*44*	*0.086*
no (n=109)	109	*52*	27	*43*	82	*56*	
General attitude towards the risk (means ± SD)							
regarding their personal life (n=221)	5.1±2.1		4.8±2.1		5.2±2.1		*0.194*
regarding their money (n=220)	4.1±2.4		4.1±2.6		4.2±2.3		*0.922*
regarding their patients' health (n=220)	5.3±2.1		5.2±2.4		5.3±2.0		*0.630*
regarding their own health (n=219)	5.7±2.1		5.5±2.2		5.8±2.0		*0.243*
Responses to the vignettes							
MDM score (mean ± SD)	10.2±1.6		11.7±*1.4*		9.6±*1.3*		*<0.001*

SD: Standard Deviation; pts: patients; MDM: medical decision-making. Student[a] or Wilcoxon[b] tests for continuous variables; χ^2 test for categorial variables.

are ambiguity neutral, and 50 are ambiguity seeking. Regarding the Allais paradox, the AC, BD, AD and BC choice patterns were found in 90 (42.9%), 11 (5.2%), 102 (48.6%), and 7 (3.3%) assessable subjects, respectively, which represents 101 EU respondents (48.1%) and 109 non-EU respondents (51.9%). Mean self-reported willingness to take risks is 4.1 (SD±2.4) in the financial domain, 5.1 (SD±2.1) in their personal life, 5.3 (SD±2.1) for a patient's health, and 5.7 (SD±2.1) for their own health.

K-means clustering identifies two populations of physicians

From the pattern of responses to the 6 clinical vignettes, the K-means clustering (see *Online Supplementary Appendix Section III* for details) allowed us to separate two groups of physicians: one group of clinicians with lower MDM-scores, i.e. more likely to choose intensive therapy (IC group), and another group of clinicians with higher MDM-scores, i.e. more likely to choose non-intensive therapy (Non-IC group).

IC-physicians harbor specific behavioral characteristics compared with non-IC-physicians

A bivariate comparison of the characteristics of physicians in the IC and Non-IC groups is summarized in Table 2. We detected significantly more aversion toward uncertainty within the IC cluster (mean certainty equivalents of 228 euros for the Non-IC group *vs.* 276 euros for the IC group; P=0.031) (Table 2). For the Allais paradox, we detected a trend toward significance (P=0.086) with more EU subjects in the Non-IC group (57%) than in the IC group (44%). Among the demographical and occupational characteristics, only the patient volume was associated with these clusters, with a mean number of older AML patients treated annually of 19.1 in the IC group *versus* 24.5 in the non-IC group (P=0.03). Although we found more male and risk-averse physicians in the IC group, these differences were not significant (P=0.06 and P=0.131, respectively).

The logistical regression of the IC *versus* non-IC groups, on individual characteristics that were significant with a P-value <0.20 in the bivariate analysis, is presented in Table 3. This analysis confirmed that aversion towards uncertainty increases the probability of belonging to the IC group [OR (95%CI): 1.17 (1.01;1.37); P=0.043] and that higher patient volume increases the probability of being in the non-IC group [OR (95%CI): 0.98 (0.96;0.99); P=0.032]. We found an interaction between gender and the Allais paradox resulting in a statistically significant increase in the probability of being pro-IC among men who do not conform to the Expected Utility model [OR (95%CI): 3.45 (1.34;8.85); P=0.01], but such an effect was not found among women.

Discussion

In this cross-sectional national survey, we evaluated the impact of physicians' behavioral characteristics on their medical decision-making in older patients with AML. We hypothesized that physicians' behavioral traits such as risk and uncertainty aversion or rationality could be correlated with their choice between intensive and less-intensive therapy. To our knowledge, this is the first evidence that physicians belonging to the uncertainty-tolerant group recommend IC significantly less often than uncertainty-averse physicians, and that male physicians considered as "economically irrational" prescribe more IC.

Several non-biological factors (NBF) are known to be associated with a patient's health-related outcomes such as socio-economic status (SES), area of residence or marital status.[29,30] In the spectrum of NBFs affecting cancer patient outcomes, physician's characteristics have been described as therapy determinants in the setting of allogeneic stem cell transplantation for hematologic malignancies[12] and solid tumors.[31] In our study, neither age, hierarchical status or years of experience influenced the tendency of physicians to belong to the IC or Non-IC group, while individual uncertainty aversion was a strong determinant of practice variations in multivariate analysis. Volume-outcome relationships at treatment facility level[32,33] and at physician level[34] are well described with NBF affecting the outcome of patients with cancer. It is worthy of note that our study gets behind the volume-outcome relationship in AML, while connecting physician's patient volume with medical decision-making and more precisely with therapy intensity.

Verma *et al.*[35] stated that physicians should learn about the individual behavioral mechanisms underpinning choices under uncertainty. Our findings go one step fur-

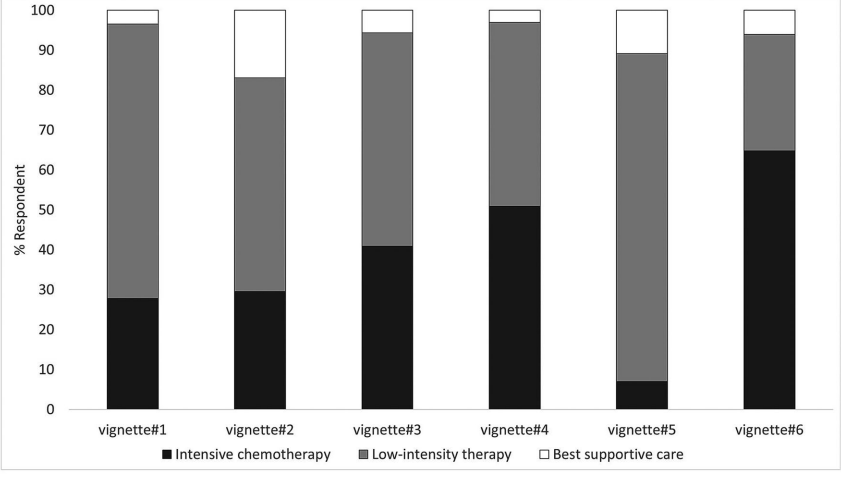


Figure 2. Medical decision-making among the 6 clinical vignettes. Proportion of physicians choosing intensive chemotherapy, low-intensity therapy or best supportive care for each of the 6 clinical vignettes.

Table 3. Characteristics associated with belonging to the intensive care (IC) group. Results from the multivariate logistic regression among the 210 clinicians for whom complete data of variable selected based on the bivariate analysis.*

	OR	[95% Confidence Interval]	P
Age (per additional year)	1.00	[0.97 ; 1.03]	0.757
Aversion towards risks	1.00	[0.99 ; 1.01]	0.875
Aversion towards uncertainty (for each 50 euro decrease)	1.17	[1.01 ; 1.37]	0.043
General attitude towards the risk regarding personal life	1.10	[0.95 ; 1.29]	0.208
Activity in AML pts. ≥60y/year	0.98	[0.96 ; 0.99]	0.032
Gender among rational			
Men	ref.		
Women	0.93	[0.39 ; 2.20]	0.865
Expected utility among men			
Yes	ref.		
No	3.45	[1.34 ; 8.85]	0.01
Interaction term = difference between irrational effect among women and men	0.253	[0.07 ; 0.91]	0.035

OR: Odds Ratio; pts: patients; AML: acute myeloid leukemia; ref: reference value. *Results of the parsimonious model constructed from a backward-stepwise-procedure (see the Methods section for details) which was initially additionally adjusted for clinicians' general attitude regarding their own health and aversion towards risks.

ther and show that a behavioral characteristic such as uncertainty aversion is directly correlated with the clinician's therapeutic choice. We evaluated physician behavioral characteristics with tools validated in behavioral economics. Although such tasks may be incentivized (paid for real) in experimental economics, we decided to use hypothetical incentives following Kahneman and Tversky (1979) who claimed that: "the method of hypothetical choices emerges as the simplest procedure by which a large number of theoretical questions can be investigated. The use of the method relies on the assumption that people often know how they would behave in actual situations of choice, and on the further assumption that the subjects have no special reason to disguise their true preferences". Concerns have been raised about the correlation between a clinician's medical behavior and their uncertainty aversion as measured by economical tools in a non-domain-specific manner.[36] Our study confirms, as previously reported,[17,18] that economic behavior and its underlying psychological traits can predict medical behavior. Our cohort was globally risk-seeking and ambiguity-averse; 109 (51.9%) of the physicians did not conform with the EU model, which is in line with evidence in behavioral economics.[37,38] Mean self-reported willingness to take risks was consistent with previous results but higher for the patient's health domain.[39] This finding may be explained by the toxicity related to the intensive therapy that physicians are used to prescribe. We detected an interaction between physician's gender and the Allais paradox, with an impact of departures from the EU model on decision-making, in male physicians. Gender effect for risk and uncertainty attitudes is a well-established stylized fact in behavioral economics,[40,41] albeit the impact of the interaction between gender and Allais paradox on MDM has, to our knowledge, never been documented empirically.

Although our findings provide novel insights into the clinical debate pitting intensive *versus* low-intensity approaches for older patients with AML, we acknowledge that our study has limitations. The respondent panel was representative of the surveyed French hematologist population in terms of gender, hierarchical status and geographical area. Respondents more often belonged to academic centers than surveyed physicians, which can be explained by the French healthcare system's organization for AML patients usually being oriented towards academic centers. Physicians were asked to recommend how to treat an AML patient in an experimental framework. We deliberately proposed clinical situations where patients had announced they would accept medical decisions, and patient choices did not appear in the vignettes. Since informed decision-making has emerged as the new normative standard for health care,[42] concerns about the increase in complexity provided by this mode of decision making have been raised.[43] To encompass this increase in complexity, and presumably of uncertainty, physicians were asked to state which therapy they would ideally recommend, irrespective of the patient's choice. We also evaluated individual clinician's choices, whereas multidisciplinary team (MDT) decision-making is currently the standard of care in cancer. Even though a treatment plan devised by an MDT may differ from that of a single physician, it is noteworthy that the MDT constitutes an area of exchange between healthcare professionals where they may clearly state which treatment they consider to be appropriate in any clinical situation. Another limitation is the construction of the clinical vignettes. We focused the proposed treatments on intensive, low-intensity therapy and best supportive care, and did not propose any investigational drug or therapeutic strategy through clinical trial enrollment. We anticipated this would have swayed the physicians' answers in favor of trial participation. Even though clinical trial enrollment remains an ideal scenario for all AML patients, real-life data provided by the Netherland's registry show that only a small number of patients over 60-years of age could benefit from such innovative strategy.[44] We did not provide any potentially druggable molecular markers such as *FLT3*-ITD, *NPM1* or *IDH1/2* in the clinical scenarios, because, to date, a large proportion of French centers do not have access to these

markers during front-line therapeutic decision-making. The increasing use of next generation sequencing (NGS) technologies in AML will soon allow the identification of molecular markers in almost all patients, which will have various consequences. For patients with an actionable molecular marker,[45] or with accurate genomics-based outcome prediction,[46] NGS technologies will presumably reduce treatment uncertainty. Alternatively, for patients with a non-actionable marker or markers with unknown prognostic significance, NGS will likely add another level of uncertainty. Even though the MDM process cannot be restricted to a computational process, novel methods such as decision-making tools supported by knowledge banks of matched genomic-clinical data[47] are warranted. They will help physicians absorb large amounts of complex information and likely act as moderators of uncertainty. Pending the validation of such tools in daily practice, our study (which found a strong physician-effect on treatment decisions) should encourage the use of validated prognostic scores to rationalize the decision-making process in this setting.[48] It should also encourage further exploration of the role of physicians' attitudes in decision-making.

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