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ORIGINAL ARTICLE

Oncology nurse phone calls halve the risk of reduced dose intensity of immunochemotherapy: results of the randomized FORTIS study in chronic lymphocytic leukemia.

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Abstract

Delivering of > 80% planned relative dose intensity (RDI) of fludarabine-cyclophosphamide-rituximab (FCR) is key to benefit from longer progression free survival (PFS) and survivals in CLL. In this randomized trial, we sought to investigate whether a telephone intervention strategy (called AMA) delivered by an oncology nurse could reduce the risk of RDI < 80% by alleviating adverse events and supporting patients' adherence. Sixty FCR patients were randomized 1:1 for AMA (stratified on Binet stage C). As per guidelines, patients received pegfilgrastim as primary prophylaxis of febrile neutropenia. At the end of therapy, RDI < 80% was reported in 31% of patients, shortening PFS (median 26 months versus not reached, $P = 0.021$) and OS at 3 years (100 vs 70%, $P = 0.0089$). Oncology nurse interventions tended to significantly reduce this event (RDI < 80%: 41.4% in non-AMA versus 20.7% in AMA patients ($p = 0.09$)). By adjusting our logistic regression model on published parameters exposing to RDI < 80%, we found that AMA protected significantly against the risk of reduced RDI (OR = 0.22, IC95% 0.05–0.84, $p = 0.04$), independently of grade 3/4 neutropenia (< 15% per cycle) and febrile neutropenia (< 5% per cycle) events. As a conclusion, we confirmed that > 20% reduction of FCR dose-intensity was detrimental for PFS/OS, but that oncology nurse interventions reduced the risk of dose concessions.

Keywords Relative dose intensity · CLL · Immunochemotherapy · Oncology nurse · Survivorship

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Introduction

The combination of fludarabine-cyclophosphamide-rituximab (FCR) is widely accepted as the standard frontline chemoimmunotherapy in chronic lymphocytic leukemia (CLL) patients, without deletion 17p/TP53 mutation [1]. FCR yields significantly higher overall response rates, minimal residual disease (MRD) eradication rate, and ultimately longer PFS and OS than FC without R in the CLL8 trial [2, 3]. Respect of *planned* relative dose intensity (RDI) is nonetheless key to really benefit from prolonged PFS and OS. *Unplanned* dose concessions (due to physician/patient will, adverse events including hematological, gastrointestinal and infectious toxicities [3, 4]) jeopardize these outcomes. Reduction of planned RDI is acceptable in selected patients, with many different trials supporting the use of low-dose FCR [5], or 4 courses of FC and 6 cycles of R (FC4R6 [6]), in elderly patients to avoid excess of toxicity. As a consequence, the median PFS were very comparable to that published with

bendamustine-rituximab (BR) regimen [3]. In real-life practice, BR, or even chlorambucil-based immuno-chemotherapies are preferable to a reduced-dose FCR, at least in terms of side effect.

The frequency of *unplanned* RDI reductions is thought to be between 33% (CLL8 and CLL10 trials from the German CLL group [7]) and 51.4% (our experience with relative dose intensity in 106 community-based patients [8]). Three factors predicted the risk of reduced RDI in the former study: age > 60 years, Binet stage C, and beta2-microglobulin > 3.5 mg/l. In the latter study, dose concessions were more based upon physician's decision (52.7%) and less because of toxicity or impaired renal function. This study also showed that the use of G-CSF was made again at the discretion of physician (57.5%) but did not impact RDI or outcomes despite significantly reducing the risk of grade 3–4 neutropenia and neutropenic fever events.

These data suggested that besides patient-related factors, therapy-related factors (side effects) but also physician-related factors all contribute to adherence to recommendations of RDI. Support programs should be targeted both to patients and their treating physicians, often not aware of fine-tuning FCR doses. These "non-compliant" prescribers are found especially outside University Hospitals, but heterogeneity of practices also emerges according to type of specialty (hematologist or oncologist), age, gender, and size of doctors' teams (usually small in the private practice in France). Since 2006, we developed a patient-empowerment program called AMA (ambulatory patients medical assistance) delivered as programmed phone calls (1–2 per week between chemotherapy cycles, described in ref. [9]) [9, 10]. With now > 10 years experience, we demonstrated that this program avoided many side effect and re-hospitalization thanks to early management of problems occurring outside hospital. So doing, AMA also helped physicians maintain adequate RDI of R-CHOP in DLBCL (diffuse large B cell lymphoma) patients. Overall, by educating patients, reinforcing adherence and trust to the goals of therapy, AMA improved OS in a non-randomized, retrospective study in DLBCL [10].

In the "facing obstacles to RDI through a telephone intervention strategy (FORTIS)" study, we sought to determine whether patients monitored with AMA experience less reduction of RDI. A primary prophylaxis with pegfilgrastim was proposed, to decrease the incidence of toxicities. As such, the parameter "physicians/patients will" was presumably put at the forefront of dose concession decisions.

Patients and methods

Patients and clinical trial description

This multicentric, phase 3 randomized study aimed to evaluate the impact of a telephone intervention strategy (AMA: *assistance aux malades ambulatoires*, or ambulatory patients support) to maintain adequate dose intensity of FCR. Major inclusion criteria were Matutes 4–5/5 CLL, any Binet stage, but with at least one iwCLL2008 criteria indicating a need for first-line treatment, eligible for a treatment with FCR. Eligibility criteria were no deletion 17p, clearance > 60 ml/mn (permitting dose adjustments if clearance 30–60 ml/mn), and comorbidity score CIRS-G ≤ 11. Patients must have signed informed consent, age > 18 years, ECOG PS 0–2, and confident with the use of telephone, no disabling deafness. Major exclusion criteria were Richter; relapsed CLL; contraindications to fludarabine (auto-immune cytopenia, creatinine clearance < 30 ml/mn); serologies positive for HIV, HBV, or HCV; and active bacterial, viral, or fungal infection.

We hypothesized that AMA program could reduce the risk of > 20% RDI from 40 to 10%, with a power of 80% and an alpha risk of 5% (including drop-out rate of 5%), a total of 60 patients were included in 3 centers over 3 years enrollment time (starting Feb2011). These patients who received FCR as frontline therapy in different settings (university and general hospitals, clinical practice) were randomized 1:1 for AMA (stratified on Binet stage C). Importantly, due to our published experience with delayed neutropenia, patients all received pegfilgrastim 6 mg SQ at day 8 of each cycle. Furthermore, trimethoprime + sulfamethoxazole and valaciclovir prophylaxes were also given to patients.

FORTIS trial was registered under the accession number NCT01393366 (sponsorship: University Hospitals of Toulouse, with a grant from Amgen).

Primary outcome was the evaluation of observed reductions in relative dose intensity, calculated as the difference between initially planned doses of F, C, and R and effectively prescribed doses of the three drugs, before and after six courses of FCR. Secondary outcome measures included evaluation of toxicity grade 3/4 (using CTCAE classification v4.0, time frame: 3 years), rate of grade 3/4 toxicities (neutropenia, fever, infections, renal insufficiency), assessment of quality of life, and psychological comfort during FCR therapy.

Reduction of dose intensity (RDI), overall response rates, calculation of outcomes

Doses of FCR were calculated from either pharmacist and/or oncologist records, in comparison to the standard FCR doses (=planned DI): oral F 40 mg/m^2 3 days, C 250 mg/m^2 3 days, and R 375 mg/m^2 day 1 cycle 1, then 500 mg/m^2 day 1 for cycles 2 to 6. At the end of the planned time of therapy (24 weeks for 6 cycles), RDI (mg/m^2/week) was calculated as the ratio of the amount of F, C, or R actually delivered (=actual DI for each drug) to the planned DI for the fixed time period of 24 weeks. Reduction of DI (RDI) was considered if less than 80% of the planned DI was delivered, based on our

published threshold [7], validated in the CLL8 and CLL10 trials [6].

Three months after the last FCR cycle, overall response rate was assessed as partial response (PR), since no bone marrow biopsy was done to classify patients as CR (or CR with incomplete bone marrow recovery), in accordance with the IwCLL2008 criteria [11]. Progression-free survival (PFS) and overall survival (OS) were calculated from the first day of the last FCR cycle until relapse/death or death from any cause, respectively.

Statistical analyses

Survival curves were plotted according to Kaplan-Meier analysis and compared using the log-rank test. Percentages were compared using either chi2 or Fisher's exact tests, medians were compared using the non-parametric Mann-Whitney analysis. A multivariate logistic regression model (adjusted on age, Binet, gender) was used to evaluate the impact of AMA on RDI.

Results

Overall response rates, progression-free survival, and overall survival

Patients' characteristics are summarized in Table 1. Sixty patients were included (median age 68 years), but 58 were assessable for total DI calculation (1 progressed after 2 cycles and 1 developed AIHA after signing informed consent and did not received FCR as planned). Briefly, 81% males were included, with good renal function in 82.8%, stage C disease in 37.9%, bulky disease in 32.8%, deletion 11q in 13.8%, and complex karyotype (≥ 3 abnormalities) in 51.7%. Clinical and biological characteristics were well balanced between AMA and non-AMA arms, except for the burden of comorbidities assessed by CIRS (41.4% of AMA patients had a score of 3 or more, compared to 13.8% in the non AMA arm, $p = 0.03$). A reduction of RDI > 20% was observed in 31% of patients.

A total of 98.3% (57/58) of patients obtained at least a partial response. With a median follow-up of 3 years, median PFS was not reached (36% at 3 years, Fig. 1a), neither did OS (90% at 3y, Fig. 2a) for the entire cohort. Reduction of RDI > 20% shortened both PFS (median 26 months vs not reached, $P = 0.021$, Fig. 1b) and OS (project 3y-OS 100% vs 70%, $P = 0.0089$, Fig. 2b). Other parameters impacting PFS on univariate analysis included Binet stage C (Fig. 1c), bulky disease, IgHV unmutated status, but not AMA arm, or cytogenetics. Only Binet stage C impacted OS apart from RDI (Fig. 2c).

Parameters correlated with RDI reductions: role of AMA program

By univariate analysis, risk of reduced RDI was higher in females and in anemic patients (Fisher's exact test $p = 0.05$ and $p = 0.02$, respectively), and in cases where the prescriber was an oncologist (not an hematologist, 13.9% vs 41.7%, $p = 0.04$). Other factors had no impact on RDI reductions: age > 70 years, CIRS ≥ 3, creatinine clearance, cytogenetics, Binet stage C, neutrophils/platelets/lymphocytes count, type of private/public practice, and size of doctors' team.

The primary analysis of this study could not demonstrate a reduction of the risk of RDI < 80% from 40 to 10% thanks to the AMA procedure. Using a univariate logistic regression model, AMA program only tended to decrease the risk of dose reductions (from 41.4 to 20.7%, $p = 0.09$). By adjusting the model on the variables also found in the German FCR studies as predictive of dose reductions [6], age > 60, gender, renal function, and Binet stage C, AMA program significantly reduced the risk of RDI (OR = 0.24, IC95% 0.05–0.91, $p = 0.05$), while Binet stage C and female gender remained associated with an increased risk of dose reductions. This data emphasized that AMA program halved the risk of reduced dose intensity > 20% (Table 2), despite the small size of the cohort (as exemplified by our large confidence intervals), but failed to demonstrate an independent impact on PFS or OS.

Management of toxicities: impact of pegfilgrastim and AMA

As compared to published literature, pegfilgrastim prophylaxis at day 8 drastically decreased the frequency of grade 3/4 neutropenia (22% during 1st cycle weekly monitoring, but always < 20% in the subsequent cycles) and febrile neutropenia (< 10% across cycles) (Figs. 3 and 4). AMA program generated 544 phone calls (median 20 per patient), resulting in management of unexpected toxicity (transfusion, infection work-up, hospitalization) in 27.6% of cases. The family doctor was contacted at least once in 69% of patients. Due to a better reporting of AE, rates of any grade infections and febrile neutropenia were found to be higher in the AMA arm (Fig. 4).

Discussion

In this small cohort, we have addressed the everyday practice question as to whether oncology nurse intervention strategy could improve the rate of patients receiving adequate dose of FCR in the treatment of their CLL. Because experience of toxicity (or expectation of) toxicity usually explains dose reductions, we also added primary pegfilgrastim prophylaxis to limit the risk. Still, since we had heterogeneous population of recruiting physicians, we again reported a high rate of dose

Table 1 Patients' characteristics according to randomization arm

Characteristics of population	Non-AMA		AMA		Total		Chi-square test *p* value
	N = 29	100.0%	*N* = 29	100.0%	*N* = 58	100.0%	
Age (years), median [min; max]	68 [55, 78]		68 [50; 76]		68 [50; 78]		0.85
Gender							
Male	23	79.3	24	82.8	47	81.0	
Female	6	20.7	5	17.2	11	19.0	0.74
Comorbidities							
CIRS							
Not stated	2	6.9	0	0.0	2	3.4	*0.03*
< 3	*23*	*79.3*	*17*	*58.6*	40	69.0	
5 3	*4*	*13.8*	*12*	*41.4*	16	27.6	
Creatinine clearance							
Median [min; max]	79 [45;123]		75 [49;104]		78 [45;123]		0.43[b]
Not stated	1	3.4	0	0.0	1	1.7	0.47
< 60 m1/mn	7	24.1	5	17.2	12	20.7	
≥ 60 ml/mn	21	72.4	24	82.8	45	77.6	
Hypoglobulinemia							
Not stated	3	10.3	3	10.3	6	10.3	0.58
No	13	44.8	11	37.9	24	41.4	
Yes	13	44.8	15	51.7	28	48.3	
CLL-related risk factors							
Binet stage							
A	3	10.3	2	6.9	5	8.6	0.62[a]
B	17	58.6	14	48.3	31	53.4	
C	9	31.0	13	44.8	22	37.9	
Lymph node/spleen size 55 cm							
≤ 5 cm	19	65.5	19	65.5	38	65.5	1.00[a]
> 5 cm	9	31.0	10	34.5	19	32.8	
Not stated	1	3.4	0	0.0	1	1.7	
FISH results:							
Deletion 13q	7	24.1	6	20.7	13	22.4	1.00[a]
Trisomy 12	6	20.7	4	13.8	10	17.2	
Deletion 11q	3	10.3	5	17.2	8	13.8	
Cytogenetics							
Not stated	2	6.9	2	6.9	4	6.9	1.00
Non-complex	12	41.4	12	41.4	24	41.4	
Complex	15	51.7	15	51.7	30	51.7	
IGHV mutational status							
Not stated	6	20.7	10	34.5	16	27.6	
Unmutated	8	27.6	11	37.9	19	32.8	
Mutated	15	51.7	8	27.6	23	39.7	0.13[a]
Type of management of patients							
Center of care:							
University hospital	15	51.7	12	41.4	27	46.6	0.45[a]
General hospital	9	31.0	14	48.3	23	39.7	
Private practice	5	17.2	3	10.3	8	13.8	
Prescriber:							
Hematologist	19	65.5	21	72.4	40	69.0	0.82[a]
Oncologist	8	27.6	7	24.1	15	25.9	
Internal medicine	2	6.9	1	3.4	3	5.2	
Practice habitus:							
Alone	11	37.9	10	34.5	21	36.2	
Team	18	62.1	19	65.5	37	63.8	0.78[a]
Reduction of dose intensity							
≤ 20%	17	58.6	23	79.3	40	69.0	0.09[a]
> 20%	12	41.4	6	20.7	18	31.0	
Detailed activities of the clinical nurse:							
Number of phone calls:							
Median [min; max]	–	–	20 [6;24]		–	–	–
Interventions:							
Not done	29	100	1	3.4	30	51.7	–
New drug or imaging exam	–	–	8	27.6	8	13.8	
Referal to general practitioner	–	–	12	41.4	12	20.7	
Hospitalization	–	–	8	27.6	8	13.8	
Phonecalls to general practitioner:							

Table 1 (continued)

Characteristics of population	Non-AMA		AMA		Total		Chi-square test *p* value
	N = 29	100.0%	*N* = 29	100.0%	*N* = 58	100.0%	
Not stated	28	96.6	1	3.4	29	50	–
No	1	3.4	8	27.6	9	15.5	
Yes	–	–	20	69	20	34.5	

Chi square test with *p* value considered significant if <0.05

[a] Fisher test

[b] Wilcoxon non parametric test

concessions, halved by the AMA program. Our rate of 31% of patients with RDI < 80% was very similar to the 33% rate reported by the German CLL group studies (CLL8/10 trials [6]), despite a median 7 years age difference, and the use of systematic G-CSF prophylaxis (used in 40% of patients in the German trials).

Yet, from a strict statistical viewpoint, with our initial null hypothesis that AMA would reduce rate of RDI < 80% from 40 to 10%, the primary analysis of our trial failed to demonstrate an advantage of the procedure. Furthermore, despite AMA decreased the risk of reduced RDI (a critical factor conditioning PFS in our series), it was not found per se to correlate with shorter PFS or OS. We consider that numerous factors may have segregated to end up with a lack of demonstration of a significant impact of AMA on RDI here: use of G-CSF in all

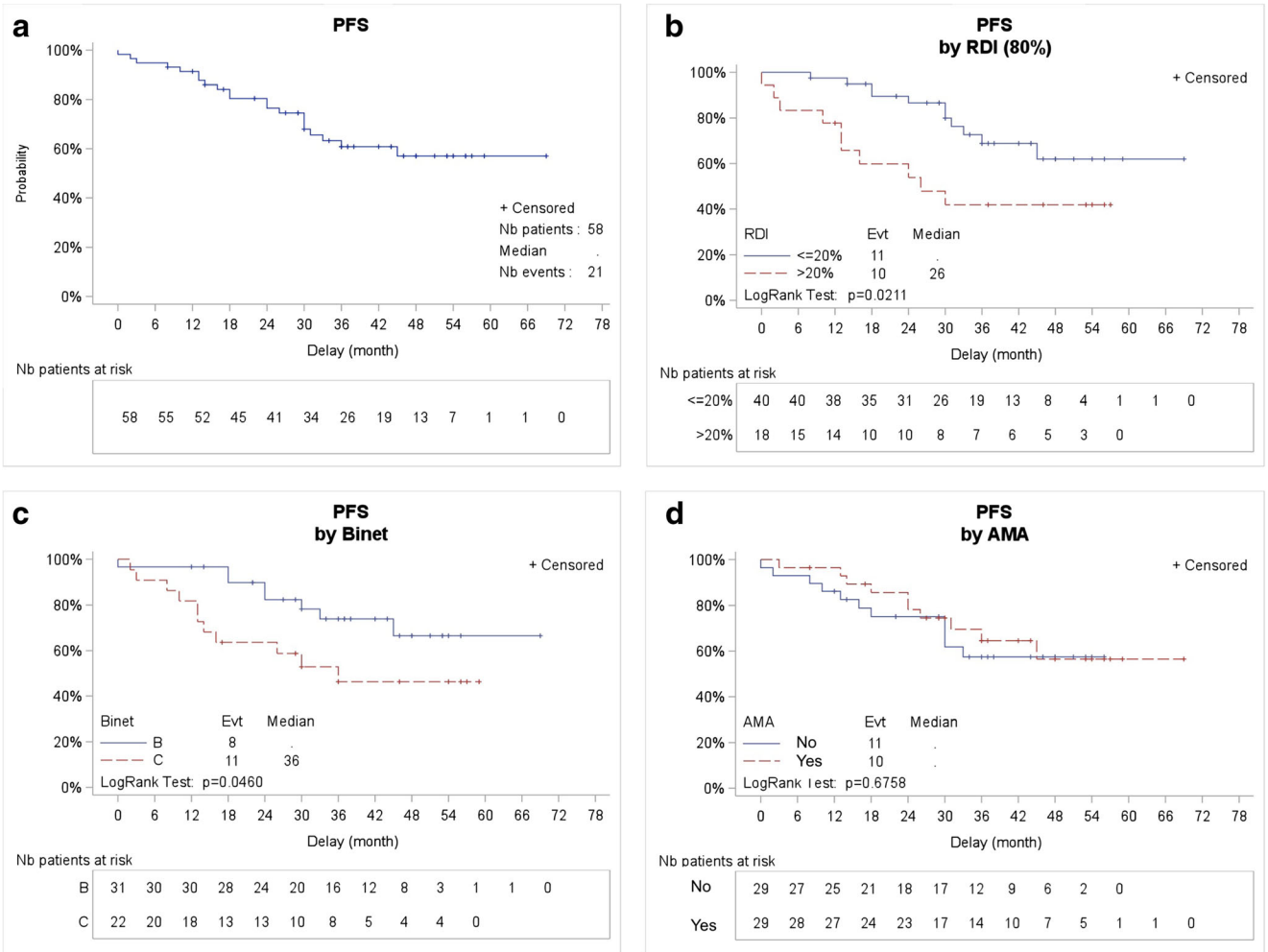

Fig. 1 Progression-free survival in 58 patients included in the FORTIS trial. **a** PFS for the entire population. **b** PFS according to dose-intensity of FCR > 80% or not. **c** PFS according to Binet stage

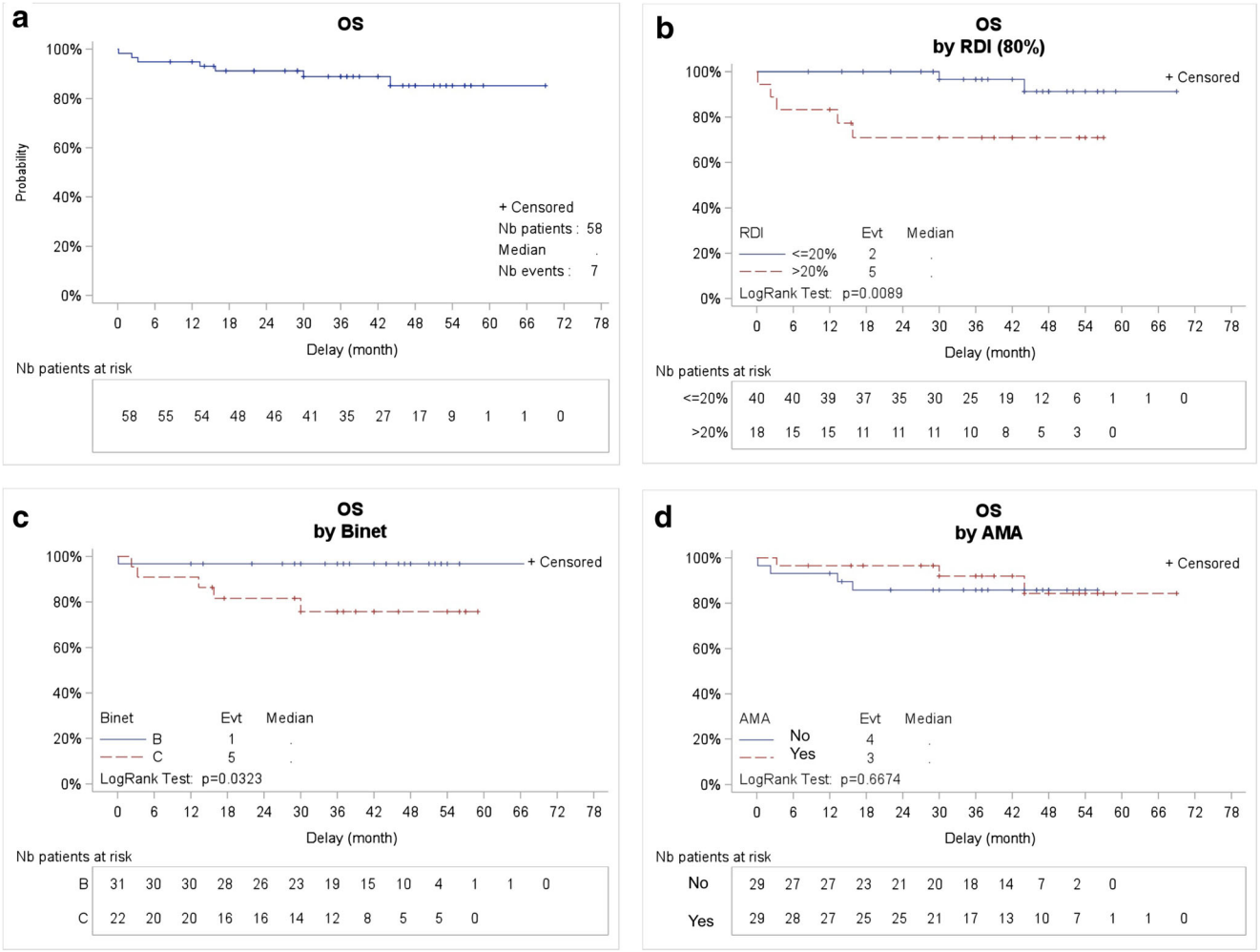

Fig. 2 Overall survival in 58 patients included in the FORTIS trial. **a** OS for the entire population. **b** OS according to dose-intensity of FCR > 80% or not. **c** OS according to Binet stage

patients, choice of FCR regimen (restricted to the most fit population of CLL patients: few comorbidities, with adequate renal function), and socio-economic status may also vary across lymphoma entities. Reduced RDI was found to be correlated with PFS in our series, confirming FCR was a dose-dense regimen, but AMA could be even more important in FCR-unfit populations, treated with less intensive strategies. On the other hand, AMA proved to be effective in detecting more thoroughly adverse events, as exemplified by the higher rate of infections observed in the AMA arm. This might be correlated to the weekly pace of phone calls capturing all mild but bothersome events, presence of symptoms like mild fever/cough being always checked by the AMA nurse (and often minimized by family doctors or patients themselves). Patients reported outcomes has become an intense area of research since the demonstration of improved efficacy and survival benefit with targeted drugs in oncology. Our nurse-delivered procedure should therefore also be evaluated in real-life trials to improve the quality of adverse event reporting.

Table 2 Factors correlated with dose reductions > 20% in our multivariate model

Parameter	OR	IC95% (lower)	IC95% (upper)	*P* value
AMA	0.24	0.05	0.91	*0.05*
Age > 60	3.18	0.48	29.53	0.25
Binet stage C	6.53	1.67	31.6	*0.01*
Creatinine clearance	1.03	0.99	1.08	0.16
Gender	5.58	1.04	36.08	*0.05*

P values in italics are 0.05 or lower

In our previous studies in DLBCL, we showed that higher RDI observed in the University Hospitals was not correlated to patient's characteristics or treatment, but to nurse phone calls (AMA program) proposed *only* to UH patients in our regional Oncology Network [11]. In this life-threatening disease, dose-dense therapy is widely accepted, referral to University Hospital hematologist

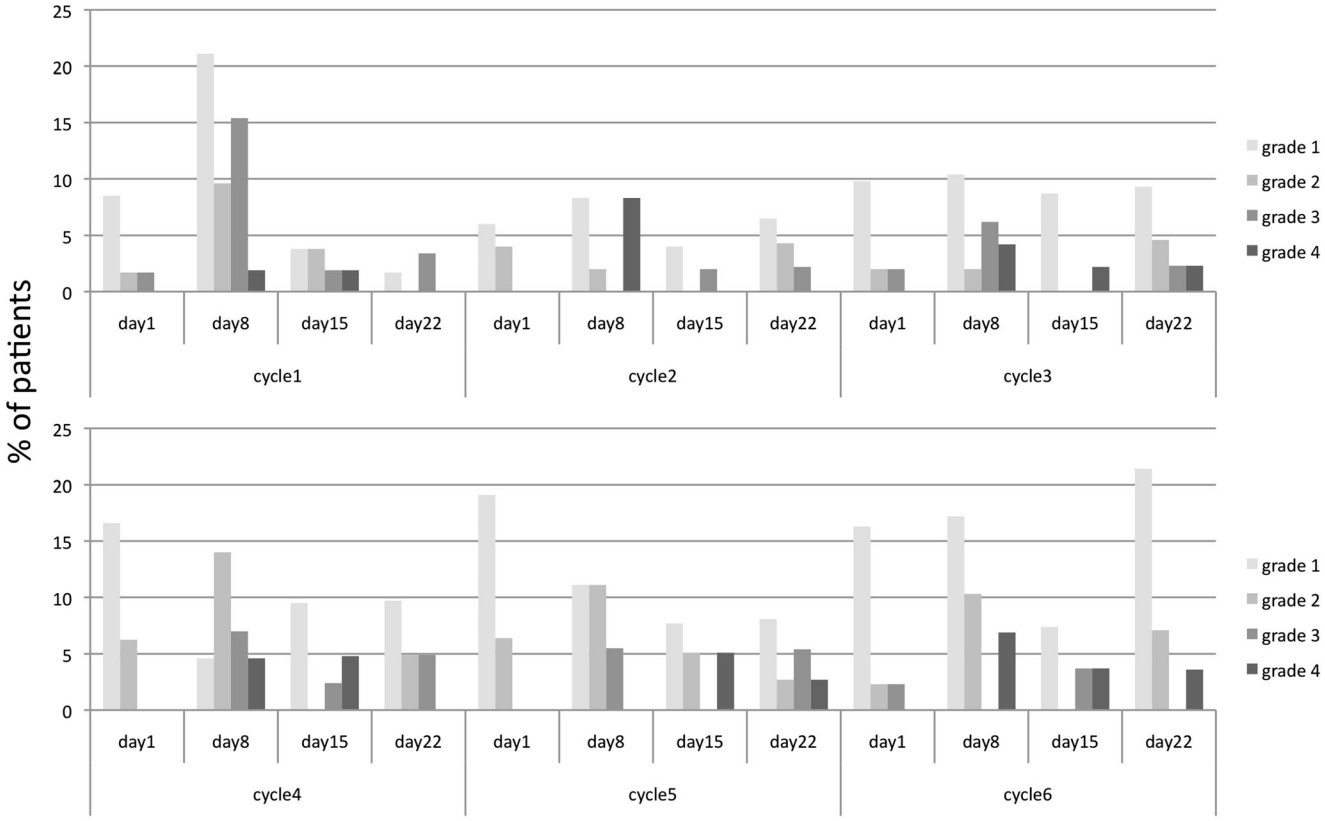

Fig. 3 Frequency of neutropenic episodes (all grades) at each FCR cycle

promoted for young patients, and dose reductions avoided. On the other hand, CLL patients are most often managed by oncohematologists in general hospital practice, and dose intensity was not observed in 41% of cases outside oncology nurse interventions. The latter most favorably impacted prescriptions of oncologists (rather than hematologists) decreased the risk of reduced RDI to 21%, not enough yet to impact PFS or OS. Patients referred to their proximity hospital, especially in non-urban areas, do not benefit from similar outcomes than patients treated in urban university hospitals (UH) with a bigger volume of patients [12, 13]. However, the underlying mechanisms of reduced OS remain unclear. Many factors induce outcome disparities in the treatment of lymphoma, including non-medical factors including age, ethnic group, socioeconomic status (SES), distance to the care center, and place of residence [12–15]. Despite that we demonstrated a protective role of AMA against reduced DI, these programs alone cannot explain for prolonged PFS/OS. Disease intrinsic factors such as complex caryotype, unmutated IGHV status, also strongly contribute to outcomes. At least, we can favorably improve the chances to benefit from adequate dose prescriptions through our telephone intervention strategy. We do not know whether such nurse-delivered program is transferable to other hospitals, but different UH centers in France started to evaluate the impact on RDI in both DLBCL and CLL patients. Nurse interventions, by reducing the burden of unplanned and/or unnecessary use of medical resources, including re-hospitalizations, are medico-economically relevant at the era of modern chronic cancer therapy.

It is important to emphasize that our study also suggested an interest of using long acting G-CSF with a slight modification of injection date (day 8 instead of day 4). Long acting G-CSFs (like pegfilgrastim) are dosed once and improve convenience to patients, compliance, and have shown better results and outcomes than with filgrastim (replacing 8–12 days of standard G-CSF). According to international ASCO/ASH guidelines [15, 16], > 20% risk of febrile neutropenia warrants the use of such prophylaxis. In our previous report, nadir of neutropenia occurred between days 15 and 22 after FCR, so we chose to use pegfilgrastim at day 8 for a full coverage of this period in all patients. Administration of such long-acting G-CSFs has been confirmed to be optimal at least > 24 h after chemotherapy [17]. The low percentage of CR with incomplete bone marrow recovery suggested this option was safe for normal myeloid progenitors, and the low rate of febrile neutropenic events per cycle (5% or less) confirmed also the efficacy of this strategy. Still, and unexpectedly with previous publications, G-CSF did not prevent 31% of prescribers from decreasing RDI of

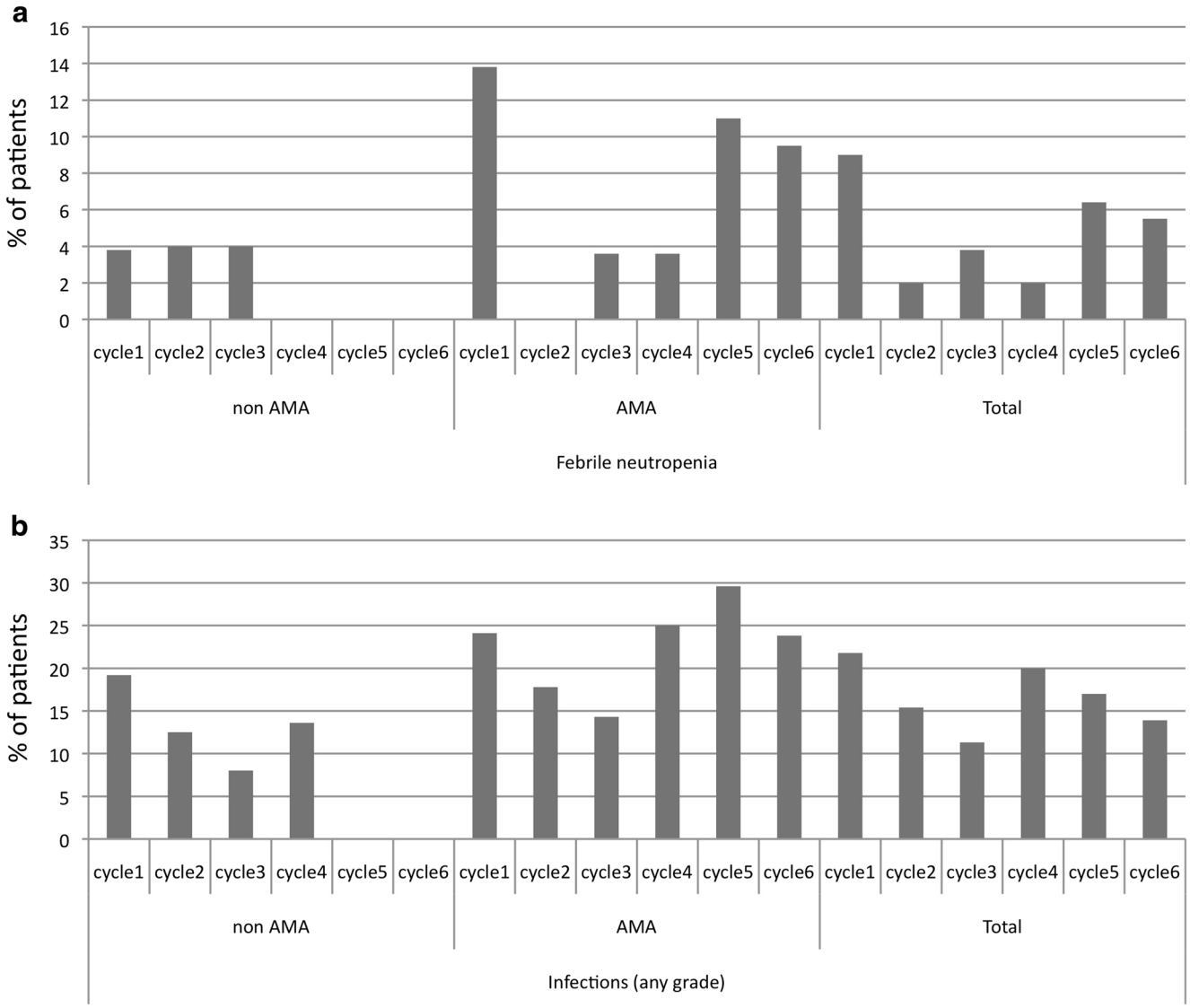

Fig. 4 Frequency of febrile neutropenia (**a**) and infections of any grade (**b**) at each FCR cycle, according to randomization arm

FCR of at least 20%. By adjusting our statistical model to variables found to be correlated to reduced DI of FCR in German CLL group CLL8 and CLL10 trials, we still found an advantage of AMA in reducing the risk of dose reductions (76%). On the other hand, the frequency of grade 3–4 hematological toxicities at cycle 5 and 6 despite AMA, together with the recent publication of the French CLL group sponsored CLL2007SA trial (which confirmed excellent results of giving 4 cycles of FC and 6 cycles of rituximab, to spare 2 FC cycles) [6], prompted us to adopt the FC4R6 regimen with pegfilgrastim day 8 cycles 1–4, and AMA delivered on cycles 1–6 weekly, as the best option to deliver FCR with the optimum chances for MRD eradication and prolonged survivals in patients above 65 years.

As a conclusion, our randomized study, though a limited number of patients were included, showed how a telephone intervention strategy might support the DI of FCR in CLL frontline. Despite the use of pegfilgrastim that dramatically reduced the risks of grade 3/4 neutropenia and especially febrile neutropenia, prescribers and/or patient support systems are still warranted to maintain full dose delivery of this gold standard therapy.

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Compliance with ethical standards

Conflict of interest LY has received research grants from Janssen and Roche, and speaker honoraria from Janssen, Roche, Gilead, Abbvie. All the other authors declare not to have received any financial support for this study.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual patients included in the study.

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