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Effectiveness of telephone support during chemotherapy in patients with diffuse large B cell lymphoma: The Ambulatory Medical Assistance (AMA) experience

Gisèle Compaci [a], Loic Ysebaert [a,*], Lucie Obéric [a], Hélène Derumeaux [b], Guy Laurent [a]

[a] Service d'hématologie clinique, CHU Purpan, 1 place du Dr. Baylac, F-31300 Toulouse, France
[b] Département d'Informatique Médicale, Hôtel-Dieu, 2 rue Viguerie, F-31300 Toulouse, France

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ABSTRACT

Background: During chemotherapy, patients experience disabling side effects or even sometimes life-threatening treatment-related complications, contributing to poor quality of life, reduced therapeutic compliance, decreased relative dose-intensity, and ultimately poorer outcomes.
Objectives: The Ambulatory Medical Assistance (AMA) project, a monitoring procedure based on a standardized telephone intervention, was aimed to improve ambulatory care quality in aggressive B-cell lymphomas treated with standard front-line R-CHOP therapy.
Design: Non-comparative prospective study.
Setting and participants: Over a three-years period, one hundred diffuse large B cell lymphoma (DLBCL) patients were treated in a single hospital and monitored in an ambulatory setting through planned telephone interventions delivered by a single nurse under the supervision of an oncologist.
Methods: In addition to biological monitoring, patients received a bi-weekly telephone call from an oncology-certified nurse. All events were recorded on a call form, which was forwarded to a supervisor oncologist. Nurse calls resulted in one of the following: no intervention, grade 1 intervention based on a pre-established protocol managed by the nurse under oncologist supervision, or grade 2 intervention related to more severe complications, managed directly by the oncologist, and mostly resulting in secondary hospitalization.
Results: The AMA procedure consisted of 3592 phone calls (600 h) resulting in 989 interventions (27.5%). Grade 1 intervention represented 950 cases whereas grade 2 intervention was noted in only 39 cases (3.9%). AMA also appeared to improve medical management. Indeed, compared to the literature, we observed lower incidence in secondary hospitalization (6%), delayed treatment (6%), reduced relative dose-intensity (RDI) (no patient with RDI $< 80\%$), toxic death (0%), and red blood cell transfusion (13%).
Conclusions: AMA appears to improve R-CHOP therapy management. However, comparative studies are needed to demonstrate the advantage of the AMA over standard management, in terms of therapeutic compliance, progression-free survival, and medico-economics efficacy.

What is already known about the topic?

- Delivering full dose planned treatment is of upmost importance in lymphomas.
- Delivery of full chemotherapy doses on schedule nevertheless faces many obstacles in outpatient populations

* Corresponding author. Tel.: +33 561772094; fax: +33 561772177.
E-mail address: ysebaert.l@chu-toulouse.fr (L. Ysebaert).

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(e.g., infections, neutropenia, anemia, fatigue, digestive symptoms), that also compromise quality of life and compliance with treatment.
- Hematopoietic growth factors (G-CSF, epoietin) administration reduces myelosuppression but does not necessarily allow the delivery of full chemotherapy doses on schedule.

What this paper adds

- Our study demonstrates the feasibility and the effectiveness of the AMA procedure in the management of patients with aggressive lymphomas.
- Our study suggests that, compared to the literature, patients treated with R-CHOP according to the AMA procedure receive higher dose-intensity while they benefit from reduced incidence of secondary hospitalization.

1. Introduction

Non-Hodgkin malignant lymphoma (NHL) represents the 5th most frequent type of cancer in men, and the 7th in women. The most frequent subtype of NHL in adults is the diffuse large B cell type (DLBCL), accounting for 35% of NHL. DLBCL patients are best treated with CHOP combinations (cyclophosphamide, hydroxyadriamycin, oncovin, prednisone, repeated every 14–21 days) in association with rituximab in the new worldwide standard R-CHOP14 or R-CHOP21 (Coiffier et al., 2002; Feugier et al., 2005; Pfreundschuh et al., 2008). R-CHOP regimens are efficient with overall survival comprised between 80% and 50%, for low risk-patients and high-risk patients, respectively (Feugier et al., 2005), risk being defined by the age-adjusted International Prognostic Index score (aaIPI) (The International Non-Hodgkin's Lymphoma Prognostic Factors and Project, 1993). However, despite evident benefits, R-CHOP chemotherapy induces life-threatening complications. Previous studies have reported toxic death in about 6–13% of patients with R-CHOP21 (Habermann et al., 2006), R-CHOP14 (Pfreundschuh et al., 2008), or with ACVBP, a dose-dense CHOP variant (Tilly et al., 2003), now used in high risk young patients as recommended by the Groupe d'Etude des Lymphomes de l'Adulte (GELA) study group. Toxicity is even higher in older patients, especially those with high aaIPI (Thieblemont and Coiffier, 2007). Among treatment-related side effects, severe neutropenia and related sepsis remain the most critical. For example, in the German Ricover-60 study, one of the largest phase III study dealing with DLBCL, grade 3–4 leukocytopenia was found in more than half the cases, and the infection rate was about 30% despite the use of granulocyte colony stimulating factors (G-CSF) such as filgastrim or lenogastrim (Pfreundschuh et al., 2008). Second, R-CHOP may induce less severe but still disabling side-effects, among which constipation, nausea, vomiting, mucositis, neuropathy and cardiac toxicity are the most frequent (15% in the GELA study) (Coiffier et al., 2002).

These complications occur most often at home, between chemotherapy cycles, according to the ambulatory status of these patients. These complications not only compromise quality of life but also, in combination with psychological distress, may alter quality of heath care, including breaks in scheduled medications, omission in biological follow-up and loss of therapeutic adherence. These disturbances induce delay in chemotherapy schedules, or even treatment drop-out, resulting in decreased relative dose-intensity (RDI), the latter being an important parameter for DLBCL survival (Bosly et al., 2008; Terada et al., 2009; Hirakawa et al., 2010). Degradation of health care quality may be worse in patients with advanced age, poor social conditions, limited access to primary care providers, or living in rural areas as it has been recently suggested (Loberiza et al., 2009).

Chemotherapy side-effects are generally managed by telephone calls. Usually in most cancer centers, the patients call the oncology unit, and less commonly the primary care provider. Unscheduled patient calls, particularly when made under stress, lack reliability (e.g., patient cannot assess properly his own symptoms) and do not necessarily fit with hospital organization (e.g., MD or nurses cannot be always available on phone) (Formica et al., 2009; Marcus et al., 2002). Moreover, unscheduled calls from patients may lack urgency and cause inappropriate use of health care provider time.

All these considerations support alternative management in which the care providers call the patients to perform a medically relevant evaluation. For this reason, we designed a pilot study in which telephone follow-up was initiated by an oncology certified nurse. She collected all information relative to the patient physical and mental outcome between R-CHOP cycles, and ultimately applied a set of procedures under oncologist supervision. This care plan was termed the Ambulatory Medical Assistance (AMA) project. The specific aims of our study were to assess (i) feasibility and (ii) effectiveness of AMA for outpatient care management.

2. Methods

2.1. Patient's demographics and treatment

The study was started in December 2006 and closed in December 2009. Patients were eligible according to the following criteria: age greater than or equal to 18 years and histologically documented DLBCL after centralized pathological specimen review in our department. Participants also had to have access to and ability to use a telephone.

The study was approved by the Ethical Committee of Toulouse University Hospital. All patients gave written informed consent, according to the institutional review board procedure. Characteristics of patients are listed in Table 1. All patients included in this study lived in the area of Toulouse and vicinity, containing about 1 million inhabitants. All DLBCL patients were treated by R-CHOP21 or R-CHOP-derived protocols. R-CHOP21 (78%) was given for patients between 18 years and 60 years for either 6 cycles (if aaIPI = 0) or 8 cycles (aaIPI = 1), and for all patients between 60 and 75 years, as described by the GELA (Coiffier et al., 2002). R-ACVBP was given to patient younger than 60 years with high risk (aaIPI = 2 or 3), as

Table 1
Characteristics of our diffuse large B cell lymphoma patient population. IPI: International Prognostic Index score; M/F: male/female; R-CHOP: rituximab-CHOP (cyclophosphamide hydroxyadriamycin, oncovin, prednisone); R-ACVBP: rituximab-ACVBP (adriamycin, cyclophosphamide, vindesine, bleomycin, prednisone).

Characteristics	% of patients
Age (years)	Median 57 (20–90)
Gender M/F	57/43
Stage III–IV	34
Age adjusted IPI	
0	17
1	32
2–3	51
Treatment schedule	
R-CHOP21	78
R-ACVBP	11
R-miniCHOP	11

described previously for ACVBP (Tilly et al., 2003), in association with rituximab (375 mg/m^2 at day 1 of each cycle). Elderly patients (>75 years) were treated with lower doses (R-mini-CHOP) with 50% and 20% reduction for doxorubicin and cyclophosphamide dose, respectively, compared to standard CHOP. All patients received supportive care consisting in anti-emetics (ondansetron 8 mg tid at day 1, and then aprepitant 125–80–80 mg for 3 days), as well as antibiotic prophylaxis (sulfamethoprime–cotrimoxazole for Pneumocystosis and valacyclovir for Zoster virus infection). Ninety-nine patients received G-CSF (filgrastim or pegfilgrastim) based on European Organization for Research and Treatment (EORTC)–American Society of Clinical Oncology (ASCO) guidelines. Recombinant erythropoietin (rEPO) (epoietin beta 30,000 units per week) was started if hemoglobin count was below 10 g/dl, with systematic IV iron supplementation (Pedrazzoli et al., 2006). Red blood cell transfusion and platelets were given in case of EPO-refractory anemia (hemoglobin < 8 g/dl) or thrombocytopenia (platelet count < 10,000/dl), respectively. Reduction in RDI was calculated for cyclophosphamide and anthracycline as previously described (Pettengell et al., 2008). Response was assessed according to the International Working Group criteria: complete response (CR), complete response unconfirmed (CRu), partial response (PR), stable disease or progressive disease (Cheson et al., 1999).

2.2. AMA intervention

Before hospitalization, all DLBCL patients had a 1-h first visit with an oncologist. This was followed by an additional visit with an oncology certified nurse. This nurse was specifically dedicated to the AMA project. The nurse visit aimed to describe modalities of care (planning of hospitalization dates, biological follow-up), means of prevention and detection of side-effects, emergency patient call procedure (oncology unit hot line, oncologist and AMA nurse e-mails), and finally the AMA procedure. The AMA procedure consisted in calling patients at home at a set time and day twice a week. The duration of the call was most often about 10 min. Calls were made between Monday and Friday. The AMA follow-up was stopped after the completion of all cycles. The following information was collected on a patient call form (PCF): general status (WHO scale), temperature, weight, and symptoms according to the NCI criteria (see Appendix A). All of them were classified in great organ functions, as proposed by the NCI common toxicity criteria classification). In parallel, outpatient blood test follow-up (full blood cell counts, eventually including other tests depending on symptoms) were performed in private laboratories closest to the patient's home (twice weekly) and faxed to the AMA nurse. Biological analyses and the PCF were forwarded daily to the oncologist for information and intervention. Based on PCF, three different levels of interventions were possible: (1) *grade 0:* no intervention; (2) *grade 1:* the situation required intervention for expected non-life threatening complications, for example non-complicated febrile neutropenias, which were managed by oral antibiotics at home or changes in anti-emetic drugs (grade 1 interventions used a previously established prescription based on written protocols); and (3) *grade 2:* the situation required the direct intervention of the oncologist because of the occurrence of expected life-threatening complications (such as severe sepsis, severe digestive symptoms, lung infection, bleeding) or symptoms that required further investigation (major asthenia, unexplained abdominal pain, respiratory symptoms). From then on, the referring oncologist immediately called the patient to organize either a visit or immediate hospitalization in the hematology unit.

3. Results

3.1. R-CHOP toxicity and response

R-CHOP was toxic. Only grade 3–4 toxicity was recorded and listed in Table 2. As expected from phase III studies, 72% and 31% of patients presented at least one episode of grade 3–4 neutropenia and febrile neutropenia, respectively (Table 2). Over a total of 689 cycles of chemotherapy, we observed 359 episodes of grade 3–4 neutropenia and 68 episodes of febrile neutropenia (global risk per cycle = 10%). As depicted in Table 2, digestive symptoms were the second most common complications whereas cardiotoxicity was much less frequent (1%) (one case of reversible cardiac failure after treatment completion). Preemptive management of anemia using rEPO was started in 46% of cases, translating into a low red blood cell transfusion rate of 13% (Table 3). Response was assessable in all 100 patients. Eighty-nine patients achieved CR or CRu and 4 patients went into PR. However, 7 patients were classified as progressive disease and re-treated with either R-ICE (rituximab, ifosfamide, carboplatin, etoposide), or R-DHAP (rituximab, dexamethasone, ara-C, cisplatin), two largely used salvage regimens. Among them, in three cases, R-CHOP was prematurely stopped because of lymphoma progression. Therefore, 97 patients received the total planned cycles. One CR patient was lost after R-CHOP completion. Among the 99 followed patients, 12% relapsed within a delay ranging from one to 18 months. Four patients died, all from progression; no toxic death was observed.

Table 2
R-CHOP or CHOP grade 3–4 toxicities reported in published large studies dealing with diffuse large B cell lymphoma patients. NR: not reported. Cohorts are referenced as follows: (1) Coiffier et al. (2002); (2) Pfreundschuh et al. (2004); (3) Habermann et al. (2006); (4) Pfreundschuh et al. (2008); (5) Bosly et al. (2008).

	AMA	1	2	3	4	5
Patients	100	202	178	318	325	272
Neutropenia	72%	40%/cycle	72%	78%	48%	47%
Febrile neutropenia	31%	12%	38%	17%	53%	26%
Thrombocytopenia	28%	NR	5%	14%	NR	NR
Mucositis	5%	3%	0%	NR	7%	NR
Nausea	20%	4%	8%	NR	3%	NR
Constipation	11%	2%	NR	NR	2%	4%
Neurotoxicity	9%	5%	3%	NR	41%	32%
Nephrotoxicity	2%	1%	1%	NR	5%	NR
Cardiotoxicity	1%	8%	NR	9%	2.5%	NR
Toxic death	0%	6%	3%	5%	8%	NR

3.2. AMA and telephone intervention

AMA procedure resulted in 3592 phone calls for the entire cohort, thus accounting for approximately 600 h of work for the nurse. Telephone calls generated grade 0 intervention in 2642 cases, while grade 1 was noted in 950 cases (26.7% of total calls). For grade 1 intervention, the need for a primary care provider was negligible (8/950). Grade 2 intervention by the oncologist was also uncommon (39/950 = 4%). Therefore, it appears that post-R-CHOP follow-up required frequent adjustments in the supportive care plan (almost 30% of patients). However, it appears that in 95% of cases, the nurse was able to perform follow-up and care management, based on her skills and the protocol, the oncologist acting only as a supervisor.

3.3. AMA and medical management

One of the critical parameters of efficacy in lymphoma therapy is dose-intensity. By improving patients' adherence to care plans, we hypothesized that AMA should reduce the secondary hospitalization rate and premature treatment drop-out, as well as limit reduction of RDI. As depicted in Table 3, only 6% of patients were re-hospitalized. In all cases, secondary hospitalization was required for management of sepsis associated or not with need for transfusions, with a mean duration of 8 days. In 6 patients, treatment was delayed (2 R-ACVBP and 4 R-CHOP21), for a mean 10.1 days. In two other patients, a 50% dose-reduction in doxorubicin and 20% reduction in cyclophosphamide (so-called "miniCHOP") were introduced instead of the last R-CHOP cycles. Therefore, 8 patients experienced reduction in RDI, but went through all scheduled cycles. Dose-intensity was calculated for patients who achieved all courses of R-CHOP or R-CHOP derived therapy (97 patients). Calculation of RDI showed that 89/97 patients (92%) received planned dose-intensity (including 82% of the R-ACVBP patients). In the remaining 8/97 patients, mean RDI reduction was as low as 6.2%. All these patients achieved CR.

Table 3
R-CHOP therapy management in diffuse large B cell lymphoma patients. NR: not reported; RBC: red blood cells; RDI: relative dose-intensity. (1) Pfreundschuh et al. (2008); (2) Bosly et al. (2008); (3) Salar et al. (2009).

	AMA	1	2	3
Patients	100	325	272	700
RBC transfusions	13%	47%	32%	NR
Platelet transfusions	2%	3%	4%	NR
Re-hospitalization for infectious complications	6%	NR	22%	22%
Re-hospitalization (total)	6%	NR	NR	29%
Mean reduction RDI		NR		
<20%	6.2%		29%	41%
>20%	0%		16%	
Treatment delays	6%		NR	36%
Treatment drop-out	4%	NR	NR	8%

3.4. AMA cost

Cost was calculated based on nurse's gross salary relative to hours spent for calls (22000 Euros), secretarial contribution (540 Euros), and phone calls (2223 Euros) for a total of 24763 Euros for management of the entire cohort, thus representing only 247.6 Euros per patient. However, further investigations are needed to assess the medico-economic benefit of the AMA procedure.

4. Discussion

In this study we describe AMA, a telephone-based follow-up procedure, based on scheduled calls to the patient's home by a skilled oncology nurse who activated a set of graduated interventions based on analysis of clinical and biological monitoring parameters and previously established protocols. The aims of AMA were to provide health care quality, to promote therapeutic adherence (by encouraging patients and by providing strict control of their plans of care) and therapeutic education, as well as to maintain patients at home, improve psychological support, and use medical resources appropriately.

The first aim of this pilot study was to investigate whether AMA was feasible and acceptable for patients. From the 100 patients who have entered into the study, all patients were on time for the call, accepted the call's 10 min maximum length and correctly answered the questionnaire contained in the PCF. Most patients considered that AMA was an important contributor to their safety as well as better understanding of their disease and treatment plan. One of the most positive perceptions of

patients was AMA's educational value, suggesting that this procedure could contribute to improving cancer patient education (Schulmeister, 1991). The popularity of AMA among non-oncology certified registered nurses, residents and senior staff was largely based on this enthusiastic feedback.

The second aim of the study was to investigate whether AMA is efficient in terms of medical management. As described above, near one third of phone calls resulted in significant modifications of the planned supportive therapies, e.g., antibiotics and anti-emetics administration, EPO dose adjustments, or complementary biological analyses. This result strongly suggests that, at least for R-CHOP therapy, it is hazardous to rely only on care plans given to patients or forwarded to primary health care providers without provision for possible modifications of supportive care. The effectiveness of the AMA procedure was also supported by its triage function. Indeed, the nurse managed grade 1 intervention in 950 cases without direct involvement of an oncologist. Assuming that these interventions would have been made by the physician staff without AMA, the medical time savings was about 1.5 h per patient over the treatment period, based on 10 min calls. AMA illustrates the capacity of an oncology certified nurse for decision making through "telephone care" (Wilson and Hubert, 2002). However, comparative studies are needed to determine whether medical time saving intervention and reducing secondary hospitalization are cost effective.

This study suggests that AMA could contribute to improve health care quality. As this study had no comparison group, it is not possible to assess directly the superiority of AMA, compared to standard management. However, comparing results with other studies show promising improvements (see Tables 2 and 3). In terms of frequency of chemotherapy-related side effects, as well as treatment modalities, our cohort was similar to those reported in the literature. Therefore, it is encouraging to note that the percentage of AMA patients who received at least one red blood cell transfusion was as low as 13%, while other studies reported much higher rates ranging from 20% to 40% (Pettengell et al., 2008; Pfreundschuh et al., 2004, 2006). We believe that this difference could be due to rEPO management (i.e., tight control of hemoglobin count).

Second, the rate of secondary hospitalization appears to be decreased as well. Indeed, in the context of R-CHOP treatment, when reported, secondary hospitalization rate is as high as 20% such as in the Belgian study based on 272 patients (Pettengell et al., 2008). In the IMPACT observational study conducted in 14 European countries and in Australia, investigators have reported 29% of unplanned hospitalization in a group of 700 patients treated with R-CHOP21 (Salar et al., 2009). We observed a much lower rate with only 6% patients hospitalized. We believe that AMA contributes to maintaining patients at home, because a significant fraction of complications remain manageable in ambulatory conditions if patients are correctly supervised.

Third, reduction of RDI was uncommon. Indeed, ninety-two patients received the planned RDI, 2 patients experienced a 10–20% reduction of RDI, and no patient experienced RDI reduction higher than 20%. These results are similar to those reported in the prospective Ricover-60 phase III study (Pfreundschuh et al., 2008). However, they are much better, when compared to retrospective studies well reflecting routine practice. Indeed, in the Belgium study, 45% and 12% of patients experienced delayed or reduced doses, respectively (Pettengell et al., 2008). In the IMPACT study, the percentage of patients achieving RDI of more than or equal to 90% was also much lower (67%) (Salar et al., 2009). Moreover, in a large retrospective study conducted in 4522 cases of aggressive lymphomas patients treated with R-CHOP, CHOP or equivalent in the USA, a RDI reduction equal or higher than 15% was observed in 40% of patients (Lyman et al., 2004). Thus, it is possible that, by acting on both physical and psychological support, AMA should have facilitated treatment compliance. Whether AMA could result in improved therapeutic benefit should be evaluated in future comparative studies.

AMA relies on telephone follow-up delivered by the oncology nurse. This strategy has been applied to cancer patients to assess quality of life and psychological status at home (Nail et al., 1989; Teunissen et al., 2007). AMA represents a specific and large scale extension of these methods to the monitoring of R-CHOP therapy in DLBCL. Other technologies have been recently introduced, based on real time communication between patients and their health care providers, as illustrated by the ASyMS or video-assisted home care, or more simply, the Internet (Formica et al., 2009; Weaver et al., 2007; Kearney et al., 2009). However, at the present time, these technologies have not been validated on a large scale. However, there is little doubt that, in the near future, these methods will provide new tools in the emerging field of telemedicine applied to oncology. Nevertheless, compared to these methods, we believe that AMA offers an important advantage for patients through personalized contacts with oncology-certified nurses, who apply the knowledge they have to the benefit of their patients (Black, 2007).

Based on the results of this study, AMA appears as a feasible and effective nurse-delivered procedure for improving care organization in the context of R-CHOP therapy. We believe that AMA improves care safety, patient information, treatment compliance, all important parameters for therapy success. This advantage could be decisive in vulnerable patients because of medical, social or geographical reasons. Another important consideration is that AMA is based on the competence of specialized nurses and, as a matter of fact, features a significant step forward in the necessary competence transfer from oncologist to nurse.

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Conflict of interest: None declared.

Appendix A. Patient call form

Date of PCF			
Name	Date of birth		Weight
Day of the last chemotherapy	Treatment		Number of cycle
Patient phone number	General practitioner (GP)		GP phone

Grade NCI	0	1	2	3	4
Gastrointestinal					
Constipation					
Diarrhea					
Nausea					
Vomiting					
Mucositis					
Infections					
Febrile neutropenia					
With normal ANC					
Pain					
Neuropathy					
Dermatology					
Pruritus					
Eruption					
Renal					
Cystitis					
Pulmonary					
Dyspnea					
Cough					
Hematology					
Hemoglobin					
Platelets					
ANC					
Fatigue					

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