



HAL
open science

Adjunction of a fish oil emulsion to cytarabine and daunorubicin induction chemotherapy in high-risk AML

Emmanuel Gyan, Arnaud Pigneux, Mathilde Hunault, Pierre Peterlin, Martin Carré, Jacques-Olivier Bay, Caroline Bonmati, Maria-Pilar Gallego-Hernanz, Bruno Lioure, Philippe Bertrand, et al.

► To cite this version:

Emmanuel Gyan, Arnaud Pigneux, Mathilde Hunault, Pierre Peterlin, Martin Carré, et al.. Adjunction of a fish oil emulsion to cytarabine and daunorubicin induction chemotherapy in high-risk AML. *Scientific Reports*, 2022, 12 (1), pp.9748. 10.1038/s41598-022-13626-y . hal-04756969

HAL Id: hal-04756969

<https://nantes-universite.hal.science/hal-04756969v1>

Submitted on 28 Oct 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.





Distributed under a Creative Commons Attribution 4.0 International License



OPEN

Adjunction of a fish oil emulsion to cytarabine and daunorubicin induction chemotherapy in high-risk AML

Emmanuel Gyan^{1,2,3}, Arnaud Pigneux⁴, Mathilde Hunault⁵, Pierre Peterlin⁶, Martin Carré⁷, Jacques-Olivier Bay⁸, Caroline Bonmati⁹, Maria-Pilar Gallego-Hernanz¹⁰, Bruno Lioure¹¹, Philippe Bertrand¹², Nicolas Vallet^{1,2}, David Ternant¹³, François Darrouzain¹⁴, Frédéric Picou², Marie-Christine Béné¹⁴, Christian Récher¹⁵ & Olivier Hérault^{2,16}

The treatment of acute myeloid leukemia (AML) with unfavorable cytogenetics treatment remains a challenge. We previously established that *ex vivo* exposure of AML blasts to eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), or fish oil emulsion (FO) induces Nrf2 pathway activation, metabolic switch, and cell death. The FILO group launched a pilot clinical study to evaluate the feasibility, safety, and efficacy of the adjunction of a commercial FO emulsion to 3 + 7 in untreated AML with unfavorable cytogenetics. The primary objective was complete response (CR). Thirty patients were included. FO administration raised the plasma levels of eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids ($p < 0.001$). The pharmacokinetics of cytarabine and daunorubicin were unaffected. A historical comparison to the LAM2001 trial (Lioure et al. *Blood* 2012) found a higher frequency of grade 3 serious adverse events, with no drug-related unexpected toxicity. The CR rate was 77%, and the partial response (PR) 10%, not significantly superior to that of the previous study (CR 72%, PR 1%). RT-qPCR analysis of Nrf2 target genes and antioxidant enzymes did not show a significant *in vivo* response. Overall, FO emulsion adjunction to 3 + 7 is feasible. An improvement in CR was not shown in this cohort of high-risk patients. The present data does not support the use of FO in adjunction with 3 + 7 in high-risk AML patients.

ClinicalTrials.gov identifier: NCT01999413.

Acute myeloid leukemias (AML) are a heterogeneous group of hematological malignancies for which therapy is stratified according to cytogenetic and molecular prognostic factors. AML with high-risk cytogenetics leads to a dismal prognosis, is often refractory to induction therapy, and often relapses, even after allogeneic bone marrow

¹Service d'Hématologie et Thérapie Cellulaire, Centre Hospitalier Universitaire de Tours, Hôpital Bretonneau, Bâtiment Kaplan, 2, boulevard Tonnellé, 37044 Tours Cedex 09, France. ²ERL CNRS 7001, Leukemic Niche and Redox Metabolism (LNOx), Faculté de Médecine, Université de Tours, Tours, France. ³Centre d'Investigation Clinique, INSERM U1415, Centre Hospitalier Universitaire, Tours, France. ⁴Clinique d'Hématologie, Université de Bordeaux, Hôpital Haut-Levêque, Pessac, France. ⁵Service des Maladies du Sang, FHU GOAL, CRCINA, INSERM Angers, Centre Hospitalier Universitaire, Tours, France. ⁶Service d'Hématologie, Centre Hospitalier Universitaire, Nantes, France. ⁷Service d'Hématologie, Centre Hospitalier Universitaire, Grenoble, France. ⁸Service d'Hématologie, Centre Hospitalier Universitaire, Clermont-Ferrand, France. ⁹Service d'Hématologie, Centre Hospitalier Universitaire, Nancy, France. ¹⁰Service d'Hématologie, Centre Hospitalier Universitaire, Poitiers, France. ¹¹Service d'Hématologie, Centre Hospitalier Universitaire, Strasbourg, France. ¹²Laboratoire de Biostatistiques, Faculté de Médecine, Université de Tours, Tours, France. ¹³Laboratoire de Pharmacologie-Toxicologie, Centre Hospitalier Universitaire, Tours, France. ¹⁴Laboratoire d'Hématologie, Centre Hospitalier Universitaire, Nantes, France. ¹⁵Service d'Hématologie, Institut Universitaire de Cancérologie de Toulouse, Toulouse, France. ¹⁶Service d'Hématologie Biologique, FHU GOAL, Centre Hospitalier Universitaire de Tours, Hôpital Bretonneau, Bâtiment B2A, 2, boulevard Tonnellé, 37044 Tours Cedex 09, France. ✉email: emmanuel.gyan@univ-tours.fr; olivier.herault@univ-tours.fr

Study populations. Eligible patients for the FAMLY study were 18–61 years old and diagnosed with untreated AML ($\geq 20\%$ blasts) with high-risk cytogenetics, defined as $-5, 5q$ abnormalities, $-7, 7q$ abnormalities, $t(6;9)$, $11q23$ abnormalities excluding $t(9;11)$, $3q$ abnormalities, and a complex karyotype with three or more abnormalities¹⁵. Adequate liver, heart, and kidney function were required, as well as an ECOG status ≤ 2 and having signed an informed consent form. Patients with history of aplastic anemia, bone marrow transplantation, active infection, CNS involvement, or previous total body irradiation were excluded, as well as patients with a normal or favorable cytogenetic abnormality, such as $t(15;17)$, $inv(16)$, or $t(8;21)$. Hydroxyurea was allowed to wait for the cytogenetic results. The study was amended during accrual to allow for the inclusion of patients younger than 65 years, and for secondary AML (excluding therapy-related AML). Patients from the historical comparator were a subgroup with adverse cytogenetics from the daunorubicin arm of the phase III LAM2001 study¹⁵. Briefly, the inclusion criteria were non-acute promyelocytic de novo AML younger than 60 years. Adverse cytogenetics were defined as described above.

Pharmacokinetics. PK blood samples were collected from 10 patients included in the centers volunteering for the PK sub-study. Daunorubicin samples were collected through a peripheral vein distant from the central catheter into lithium heparin tubes within 1 h before and 1 h after each daunorubicin infusion, followed on D3 by sampling at 2, 5, and 10 h post-infusion. The samples were kept on ice and centrifuged at $1300\times g$ at 4° within 1 h of the blood draw. Supernatants were immediately aliquoted and frozen at $-80^\circ C$. Cytarabine PK samples were collected at baseline, on D3 (anytime), D7 (anytime), and 45 min and 2, 5, and 10 h after the end of the last cytarabine infusion. Samples were handled as described above. Cytarabine and daunorubicin plasma concentrations were measured by high-performance liquid chromatography (HPLC) as previously described¹⁸.

PUFA pharmacokinetics samples were collected in EDTA tubes before the first infusion of FO, before the 5th infusion, before the 9th infusion, and on D10 and D28. Tubes were kept on ice and centrifuged at $900\times g$ at $4^\circ C$ within 1 h of the blood draw and then immediately aliquoted and frozen at $-80^\circ C$. PUFAs were extracted from plasma by methanol transesterification and their concentration measured by gas chromatography, as previously described¹⁹.

Antioxidant response in primary cells. Primary mononucleated blood samples were available for a subset of patients at D1, D3, and D5 of treatment and sent to the FILO biobank for freezing in DMSO. Cell RNA was extracted (TRIzol®, ThermoFisher Scientific, Waltham, MA, USA), and 500 ng used for reverse transcription (SuperScript™ VIL0™ cDNA Synthesis Kit, ThermoFisher Scientific). Expression of the following genes was quantified on a LightCycler® Instrument II (Roche Life Science, Basel, Switzerland): *HMOX1*, *NQO1*, *SOD1*, *SOD2*, *SOD3*, *CAT*, *TXN*, *TXN2*, *GLRX1*, *GLRX2*, *GLRX2*, *GLRX3*, *GLRX5*, *GLRX5*, *GPX1*, *GPX2*, *GPX3*, *GPX4*, *GPX7*, *GSR*, *PRDX1*, *PRDX2*, *PRDX2*, *PRDX3*, *PRDX3*, *PRDX4*, *PRDX5*, *PRDX5*, and *PRDX6* and normalized according to the geometric mean of the expression of the housekeeping genes *ACTB*, *GAPDH*, and *B2M*²⁰. Primer sequences are presented in Supplemental Table S1.

Statistics. Our working hypothesis was that the adjunction of FO was not inferior to chemotherapy alone, without additional toxicity. A minimum CR rate of 50% would thus be possible using the Fleming one-step phase II procedure²¹ considering a CR of 72% with the LAM 2001 daunorubicin-based induction chemotherapy schedule (LAM 2001 D) in the high-risk cytogenetic group with a type I error of 5% and a type II error of 20%. Thus, if 18 of 30 patients or more obtained a CR, a phase III trial would be warranted. Given an expected death rate from induction therapy of 2.4%, the study would be halted and a data safety monitoring board consulted if three toxic deaths occurred. A sensitivity analysis comparing the efficacy and tolerance of the FAMLY study to that of the LAM 2001 trial was planned. Continuous variables were compared using the Mann–Whitney Wilcoxon test. Dichotomous variables were compared using the chi-2 or Fisher exact test. Statistical analyses were performed using IBM SPSS Statistics 20.0 (IBM, Armonk, NY, USA). Kruskal Wallis tests were performed for gene expression analysis using R software version 3.3.1 (<https://www.r-project.org/>).

Ethics. The study was conducted according to the declaration of Helsinki and approved by the Ethics Committee of Tours on February 15, 2013 and by the *Agence Nationale de Sécurité du Médicament* (ANSM) on January 08, 2013. All participants to the study were required to sign an informed consent form prior to any study-related activities. This study was registered on the ClinicalTrials.gov website under the number NCT01999413, on 13/12/2013.

Results

Patient characteristics. Between November 13, 2013 and June 17, 2016, 30 patients were included from nine French centers. The median age was 54 years (range 30–64 years) and only three patients were hyperleukocytic. Extramedullary disease was documented for one patient (3%). The FAMLY cohort was compared to 75 patients with adverse cytogenetics from the daunorubicin arm of the phase III LAM2001 study. The characteristics of patients from both cohorts are presented in Table 1.

n-3 PUFA pharmacokinetics. The sum of the DHA and EPA plasma levels showed a significant increase at 48 h after the start of the FO infusions, with a five-fold increase from 2.1 to 10.5 mg/L ($p < 0.001$, Fig. 2). After stopping FO administration, the plasma [DHA + EPA] concentration decreased to a mean level of 3.8 mg/mL by D28, significantly higher than baseline ($p = 0.006$).

N (%)	FAMILY	LAM 2001 D
All	30 (100)	75 (100)
Median age (min–max)	54 (30–64)	49 (19–60)
Male sex	18 (60)	46 (61)
WBC > 30 10 ⁹ /L	3 (10)	NR
PS 0–1	26 (87)	64 (85)
Extramedullary disease	1 (3)	NR
Secondary AML	2 (7)	0 (0)
Cytogenetics*		
Complex (≥ 3 abnormalities)	17 (57)	41 (55)
Monosomal	12 (40)	32 (43)
– 17	10 (33)	15 (20)
7q/– 7	8 (27)	30 (40)
11q23 abnormality	8 (27)	17 (23)
3q26 abnormality	7 (23)	7 (9)
5q/– 5	6 (20)	28 (37)
t(6;9)	1 (3)	2 (3)

Table 1. Patient characteristics. NR not reported, PS performance status, WBC white blood count. *The sum exceeds the total because of the presence of multiple abnormalities.

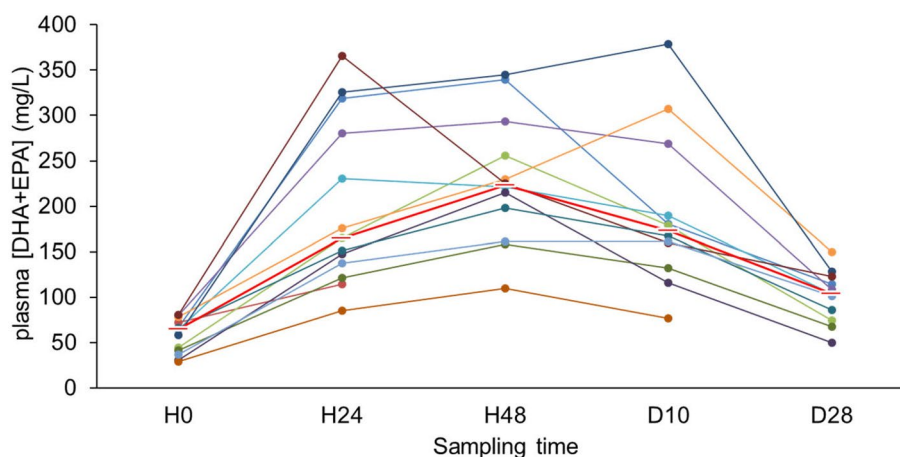


Figure 2. PUFA plasma pharmacokinetics. Plasma samples were drawn at baseline (H0), 24 and 48 h after the start of FO infusion, after the end of infusion (D10), and at disease evaluation (D28–D35). The PUFA composition of plasma was evaluated by gas chromatography. The sum of docosahexaenoic acid (DHA) and eicosapentaenoic (EPA) acid concentration is indicated for each individual patient (colored lines and dots). Means are indicated by a dash for each timepoint.

Effect of FO infusion on WBC counts in vivo. FO infusion as a monotherapy between D-2 and D1 did not reduce the WBC counts of patients without hyperleukocytosis (not shown), whereas the initiation of cytarabine + daunorubicin was associated with the rapid clearance of circulating WBCs.

Oxidative stress analysis. We observed no significant modulation of *HMOX1*, *NQO1* (Nrf-2 regulated genes), or antioxidant enzymes before or after exposure to IV FO (not shown).

Tolerance. Twenty-three serious adverse events (SAE) were declared after IV administration of FO in adjunction to 3+7 (Table 2). Most were infectious, with no modification of the study drug administration, except for one patient with respiratory failure. A detailed description of the adverse events is shown in Table 3. Of note, no liver impairment nor hemorrhagic events were observed. The mean number of days of thrombocytopenia < 20 10⁹/L was 21 (range [4; 48]) and the number of days of neutropenia < 0.5 10⁹/L was 27 (range [4; 43]). One fatal SAE was recorded but unrelated to FO. We found a higher proportion of grade 3 SAEs, associated with a lower proportion of grade 4 SAEs, when compared to the historical adverse cytogenetic group of the LAM2001 trial ($p < 0.001$).

	FAMILY	LAM2001D*	p value
Safety population	30	78	
Total declared SAEs, n	28	30	
Concerned patients, n (%)	17 (56)	25 (32)	0.02
SAEs, n (%)			
Grade 3	24 (86)	8 (27)	<0.001
Grade 4	4 (14)	22 (73)	
Grade 3–4	28 (93)	30 (38)	
Fatal, n (%)	1 (4)	8 (10)	0.44
Type of SAE, n (%)			
Infections	16	17	
Documented bacterial infections	2	4	
Documented fungal infections	1	2	
Suspected fungal infections	1		
Without documentation	3	3	
Hepatobiliary events	3	1	
Pain	2		
Cardiac events	1	1	
Vascular events	1	1	
Renal events	1	1	
Respiratory events	1	7	
Gastrointestinal events	1		
Mucositis	1		
Psychiatric disorders	1		
Cutaneous	1	2 (8.0)	
SAEs related to FO by the investigator, n (%)			
Fatal	0 (0)		
Infections	3 (66.7)		
Documented bacterial infections	2 (100) ^b		
Gastrointestinal events	1 (33.3)		

Table 2. Serious adverse events (SAEs) in patients treated in the FAMILY study compared to the daunorubicin arm of the LAM2001 study in patients with adverse cytogenetics. SAE severe adverse events. *Daunorubicin arm only. ^aOne case of mucormycosis. ^bIncluding one case of aspergillosis and one of invasive candidiasis. ^c*E. Coli* bacteriemia and *Clostridium difficile* colitis in the same patient.

	LAM2001D	FAMILY	P
N (%)	75 (100)	30 (100)	
2nd induction	37 (49)	14 (47)	0.81
CR	54 (72)	23 (77)	0.62
PR	1 (1)	3 (10)	0.14
ORR	55 (73)	26 (86)	0.11
Failure	20 (27)	4 (13)	0.11

Table 3. Response to induction in the LAM2001D and FAMILY studies. PS performance status, CR complete response, OR overall response, PR, partial response.

Daunorubicin and cytarabine pharmacokinetics during FO infusion. The C_{max} of daunorubicin was measured at 92.2 $\mu\text{g/L}$ (Q1; Q3: 44.8; 105.1), the AUC_{∞} at 414.9 ng/h, and the half-life ($T_{1/2}$) at 3.5 h, in accordance with PK data from the literature (Table 4)^{22–27} Cytarabine clearance was highly variable with a mean of 1628 L/h.

Response. All 30 patients were evaluable for CR. Twenty-three achieved a CR after induction (77%; 95%CI [61; 92]), and 3 achieved a PR (10%). Fourteen patients (47%) received the protocol-specified second induction. The CR rate was not significantly different from the CR rate of 72% in the adverse cytogenetics subgroup of the

Study	N	Drug dosing	Inf. time	C _{max} (mg/L)	AUC (ng.h)	Cl (L/h)	T _{1/2} (h)
Daunorubicin							
²⁷	4	1–1.5 mg/kg	45 min	475 ± NE	600 ± NE	NE	NE
²⁶	70	60 mg/m ²	60 min	200 ± 180	320 ± NE	270 ± 226	22.4 ± 15.4
²⁵	12	50 mg/m ²	15 min	210 ± 185	517 ± 296	221 ± 107	7.9 ± 3.0
²⁴	21	45 mg/m ²	IV bolus	NE	226 [31.6–570]	590 [90–2770]	1.5 [0.11–11.9]
²⁴	24	50 mg/m ²	60 min	105 ± NE	NE	129 ± 54	NE
FAMILY	10	60 mg/m ²	15 min	92.2 ± 82.9	415 ± 276	359 ± 15	3.5 ± 1.0
Cytarabine							
²²		200 mg/m ² /d	7d IVc	73.0 [12–266]	NE	135 ± 71	NE
FAMILY		200 mg/m ² /d	7d IVc	44.1 ± 69.8	72.1 ± 101.4	1 628 ± 1 672	10.7 ± 6.8

Table 4. Pharmacokinetics of daunorubicin and cytarabine of the FAMILY study compared to those of previous studies. Numbers between brackets indicate [min–max] when the S.D. is absent. *Inf* infusion, *IV* intravenous, *IVc* IV as a continuous infusion, *NE* not evaluated.

daunorubicin arm of the LAM 2001 trial ($p=0.63$). Propensity scoring adjustment for age differences or monosomal karyotype did not modify the CR rate.

Survival. With a median follow-up of 12.9 months for the LAM2001 study, and 7.2 months for the FAMILY study, median overall survival (not censored for allogeneic transplantation) was 13.9 months and 11.7 months, respectively, with no significant difference for the historical comparison (Fig. 3).

Discussion

The results of the FAMILY study show that the addition of IV FO to daunorubicin and cytarabine is feasible, with no unexpected toxicity. The pharmacokinetics of daunorubicin and cytarabine under FO infusion were consistent with those of previous reports in the literature, with high interindividual variability. We did not observe an in vivo effect of the FO emulsion alone on WBC count in any patient, as could have been expected based on previous ex vivo work⁶ nor an improvement in the CR rate for patients with high-risk AML. It is likely that the cell-killing effects observed in vitro in AML cell lines and primary blasts could not be reproduced in vivo because of insufficient access of PUFA to the bone marrow, even though plasma concentrations were close to those used in vitro. The novelty of our study is the demonstration that IV FO supplementation is feasible and transiently raises plasma DHA and EPA concentrations in patients with AML, and this may be useful for further applications. We also found that FO adjunction to 3 + 7 was associated with a higher proportion of grade 3 SAEs, associated with a lower proportion of grade 4 SAEs, when compared with the historical control data. However, the SAEs related to the study drug by investigator's judgment was low. This difference between the two studies is likely to be a consequence of a more stringent declaration policy in the present phase 2 trial, as compared with the LAM 2001 phase 3 trial. In the literature, an enhanced toxicity of fish oil has not been observed²⁸, rather, improved tolerability of cancer chemotherapy with the adjunction of oral PUFA has been reported in the setting of metastatic breast cancer supplemented with oral PUFA during chemotherapy⁷.

The strength of our study was the prospective evaluation of the effect of high-dose PUFA in humans with AML. One weakness of our study was the single arm design, with no 3 + 7 only comparator. This was a choice of the FILO group to launch a pilot study first and consider a comparative study if the early results of the pilot study were encouraging. As well, the two studies are 15 years apart and there have been changes in associated supportive care, and in adverse event declaration policies. This has complexified the comparison of tolerance, and does not help reach a definitive conclusion.

Overall, although EPA and DHA plasma enrichment is feasible via IV infusion of FO, we found no pharmacodynamic effect on WBC counts or oxidative stress enzyme expression and the CR rate was comparable to that of the historical study in the same high-risk AML population. It is possible that PUFAs may not have the same effect in vivo as in vitro because of the protective environment of the bone marrow niche²⁹.

The landscape of AML therapy is quickly evolving, with new agents improving the response in molecular subgroups, such as *FLT3-ITD* or *FLT3-TKD* treated with midostaurin³⁰ or *IDH1/2*-mutated AML treated with specific inhibitors^{31,32}. Interestingly, treatment of secondary AML or AML with dysplastic features with CPX-351, a liposomal formulation of 3 + 7, improves patient outcome, probably because of improved tolerability³³. In addition, combinations of low-intensity therapies, such as hypomethylating agents or low-dose cytarabine with promising candidates, such as venetoclax³⁴ or glasdegib³⁵ have shown promising results in the elderly AML population. These advances may soon be translated into the response and outcome of upfront AML therapy of younger patients. The question of whether or not the adjunction of FO formulations to modern therapies could help to improve the tolerability of emerging novel combinations, or in less aggressive hematologic malignancies, warrants further research.

Conclusion

The adjunction of FO to 3 + 7 is feasible, and the complete response rate is not inferior to standard 3 + 7. These data do not support the adjunction of FO to 3 + 7.

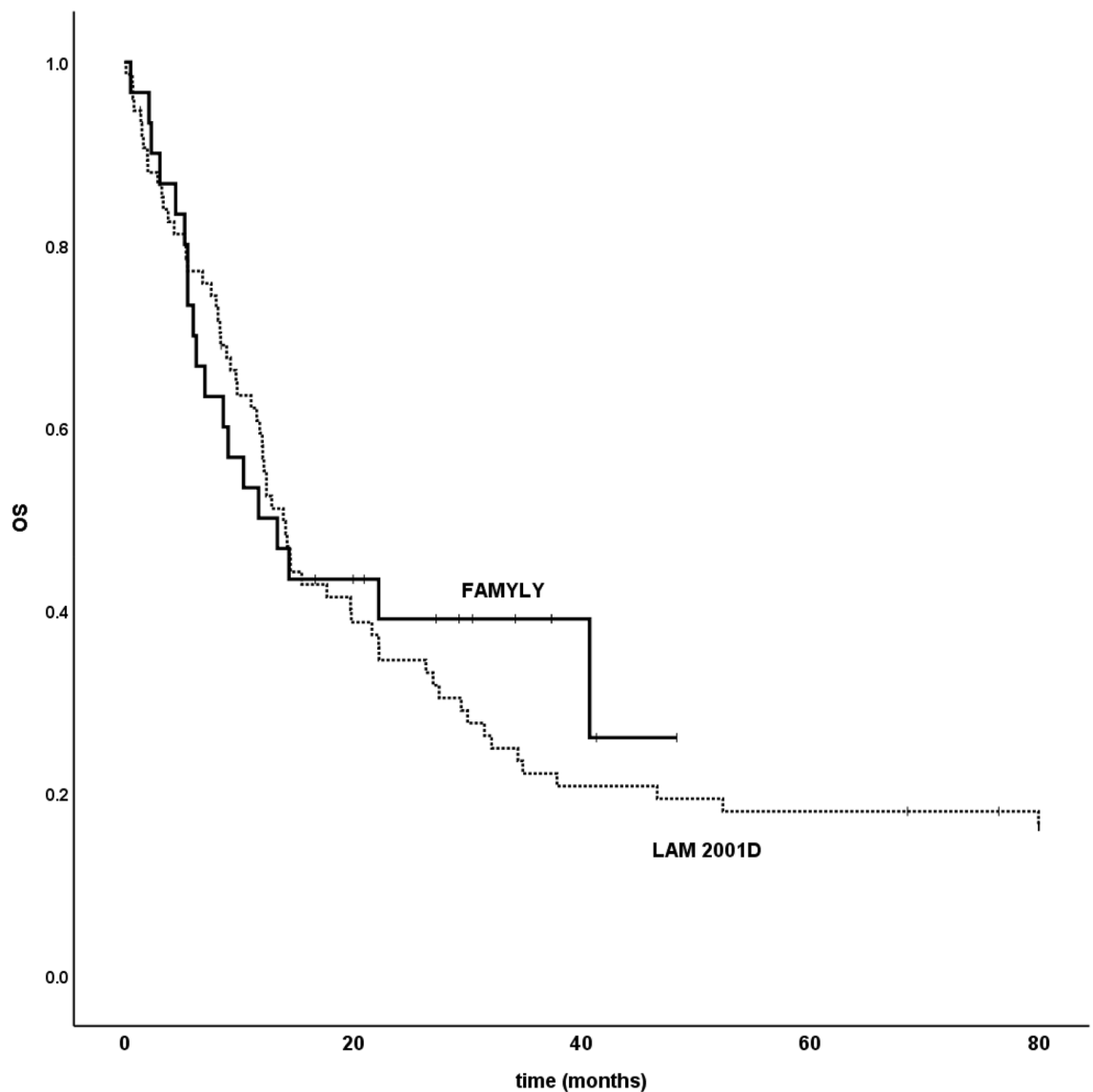


Figure 3. Historical comparison of survival data from the FAMLY and LAM2001 trials. Overall survival (OS) was plotted from the inclusion date to the date of death or last follow up. The vertical marks indicate censored observations.

Data availability

Supporting data is available on request from the authors.

Received: 28 September 2021; Accepted: 26 May 2022

Published online: 13 June 2022

References

- Song, E. & Kim, H. Docosahexaenoic acid induces oxidative DNA damage and apoptosis, and enhances the chemosensitivity of cancer cells. *Int. J. Mol. Sci.* **17**, 1257. <https://doi.org/10.3390/ijms17081257> (2016).
- Ceccarelli, V. *et al.* Eicosapentaenoic acid demethylates a single cpG that mediates expression of tumor suppressor CCAAT/enhancer-binding protein δ in U937 leukemia cells. *J. Biol. Chem.* **286**, 27092–27102. <https://doi.org/10.1074/jbc.M111.253609> (2011).
- Yamagami, T. *et al.* Docosahexaenoic acid induces dose dependent cell death in an early undifferentiated subtype of acute myeloid leukemia cell line. *Cancer Biol. Ther.* **8**, 331–337. <https://doi.org/10.4161/cbt.8.4.7334> (2009).
- Arita, K. *et al.* Mechanism of apoptosis in HL-60 cells induced by n-3 and n-6 polyunsaturated fatty acids. *Biochem. Pharmacol.* **62**, 821–828. [https://doi.org/10.1016/S0006-2952\(01\)00723-7](https://doi.org/10.1016/S0006-2952(01)00723-7) (2001).
- Aires, V. *et al.* Docosahexaenoic acid induces increases in $[Ca^{2+}]_i$ via inositol 1,4,5-triphosphate production and activates protein kinase C γ and $-\delta$ via phosphatidylserine binding site: Implication in apoptosis in U937 cells. *Mol. Pharmacol.* **72**, 1545–1556. <https://doi.org/10.1124/mol.107.039792> (2007).
- Picou, F. *et al.* n-3 Polyunsaturated fatty acids induce acute myeloid leukemia cell death associated with mitochondrial glycolytic switch and Nrf2 pathway activation. *Pharmacol. Res.* **136**, 45–55. <https://doi.org/10.1016/j.phrs.2018.08.015> (2018).

7. Bounoux, P. *et al.* Improving outcome of chemotherapy of metastatic breast cancer by docosahexaenoic acid: A phase II trial. *Br. J. Cancer* **101**, 1978–1985. <https://doi.org/10.1038/sj.bjc.6605441> (2009).
8. Hajjaji, N. & Bounoux, P. Selective sensitization of tumors to chemotherapy by marine-derived lipids: A review. *Cancer Treat. Rev.* **39**, 473–488 (2013).
9. Werner, K. *et al.* Dietary supplementation with n-3-fatty acids in patients with pancreatic cancer and cachexia: marine phospholipids versus fish oil—A randomized controlled double-blind trial. *Lipids Health Dis.* **16**, 104. <https://doi.org/10.1186/s12944-017-0495-5> (2017).
10. Shirai, Y. *et al.* Fish oil-enriched nutrition combined with systemic chemotherapy for gastrointestinal cancer patients with cancer cachexia. *Sci. Rep.* **7**, 4826. <https://doi.org/10.1038/s41598-017-05278-0> (2017).
11. Chagas, T. R. *et al.* Oral fish oil positively influences nutritional-inflammatory risk in patients with haematological malignancies during chemotherapy with an impact on long-term survival: A randomised clinical trial. *J. Hum. Nutr. Diet.* **30**, 681–692. <https://doi.org/10.1111/jhn.12471> (2017).
12. Elbarbary, N. S., Ismail, E. A. R., Farahat, R. K. & El-Hamamsy, M. ω -3 fatty acids as an adjuvant therapy ameliorates methotrexate-induced hepatotoxicity in children and adolescents with acute lymphoblastic leukemia: A randomized placebo-controlled study. *Nutrition* **32**, 41–47. <https://doi.org/10.1016/j.nut.2015.06.010> (2016).
13. Li, N. N. *et al.* Does intravenous fish oil benefit patients post-surgery? A meta-analysis of randomised controlled trials. *Clin. Nutr.* **33**, 226–239. <https://doi.org/10.1016/j.clnu.2013.08.013> (2014).
14. Barbosa, V. M. *et al.* Effects of a fish oil containing lipid emulsion on plasma phospholipid fatty acids, inflammatory markers, and clinical outcomes in septic patients: A randomized, controlled clinical trial. *Crit. Care* **14**, 1–11. <https://doi.org/10.1186/cc8844> (2010).
15. Lioure, B. *et al.* Early matched sibling hematopoietic cell transplantation for adult AML in first remission using an age-adapted strategy: Long-term results of a prospective GOELAMS study. *Blood* **119**, 2943–2948. <https://doi.org/10.1182/blood-2011-05-352989> (2012).
16. Mayer, K. *et al.* ω -3 vs. ω -6 lipid emulsions exert differential influence on neutrophils in septic shock patients: Impact on plasma fatty acids and lipid mediator generation. *Intensive Care Med.* **29**, 1472–1481. <https://doi.org/10.1007/s00134-003-1900-2> (2003).
17. Mayer, K. *et al.* Parenteral nutrition with fish oil modulates cytokine response in patients with sepsis. *Am. J. Respir. Crit. Care Med.* **167**, 1321–1328. <https://doi.org/10.1164/rccm.200207-674OC> (2003).
18. Hong, R. L. *et al.* A phase-I study evaluating the combination of pegylated liposomal doxorubicin and paclitaxel as salvage chemotherapy in metastatic breast cancer previously treated with anthracycline. *Cancer Chemother. Pharmacol.* **61**, 847–853. <https://doi.org/10.1007/s00280-007-0542-4> (2008).
19. Acar, N. *et al.* Lipid composition of the human eye: Are red blood cells a good mirror of retinal and optic nerve fatty acids?. *PLoS ONE* <https://doi.org/10.1371/journal.pone.0035102> (2012).
20. Vandesompele, J. *et al.* Accurate normalization of real-time quantitative RT-PCR data by geometric averaging of multiple internal control genes. *Genome Biol.* <https://doi.org/10.1186/gb-2002-3-7-research0034> (2002).
21. Fleming, T. One-sample multiple testing procedure for phase II clinical trials. *Biometrics* **1**, 143–151 (1982).
22. Fleming, R. A. *et al.* Clinical pharmacology of cytarabine in patients with acute myeloid leukemia: A cancer and leukemia group B study. *Cancer Chemother. Pharmacol.* **36**, 425–430. <https://doi.org/10.1007/BF00686192> (1995).
23. Krogh-Madsen, M. *et al.* Population pharmacokinetics of cytarabine, etoposide, and daunorubicin in the treatment for acute myeloid leukemia. *Cancer Chemother. Pharmacol.* **69**, 1155–1163. <https://doi.org/10.1007/s00280-011-1800-z> (2012).
24. Kokenberg, E. *et al.* Pharmacokinetics of daunorubicin as a determinant of response in acute myeloid leukemia. *Haematol. Blood Transfus.* **30**, 283–287. https://doi.org/10.1007/978-3-642-71213-5_42 (1987).
25. Galettis, P., Boutagy, J. & Ma, D. D. F. Daunorubicin pharmacokinetics and the correlation with P-glycoprotein and response in patients with acute leukaemia. *Br. J. Cancer* **70**, 324–329. <https://doi.org/10.1038/bjc.1994.301> (1994).
26. Varatharajan, S. *et al.* Population pharmacokinetics of Daunorubicin in adult patients with acute myeloid leukemia. *Cancer Chemother. Pharmacol.* **78**, 1051–1058. <https://doi.org/10.1007/s00280-016-3166-8> (2016).
27. Andersson, B. *et al.* Liquid chromatographic monitoring of daunorubicin and daunorubicinol in plasma from leukemic patients treated with daunorubicin or the daunorubicin-DNA complex. *Cancer Chemother. Pharmacol.* **2**, 15–17. <https://doi.org/10.1007/BF00253099> (1979).
28. Ma, C.-J. *et al.* Prospective double-blind randomized study on the efficacy and safety of an n-3 fatty acid enriched intravenous fat emulsion in postsurgical gastric and colorectal cancer patients. *Nutr. J.* <https://doi.org/10.1186/1475-2891-14-9> (2015).
29. Layani-Bazar, A. *et al.* Redox modulation of adjacent thiols in vla-4 by as101 converts myeloid leukemia cells from a drug-resistant to drug-sensitive state. *Cancer Res.* **74**, 3092–3103. <https://doi.org/10.1158/0008-5472.CAN-13-2159> (2014).
30. Stone, R. M. *et al.* Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. *N. Engl. J. Med.* **377**, 454–464. <https://doi.org/10.1056/nejmoa1614359> (2017).
31. DiNardo, C. D. *et al.* Durable remissions with ivosidenib in IDH1-mutated relapsed or refractory AML. *N. Engl. J. Med.* **378**, 2386–2398. <https://doi.org/10.1056/nejmoa1716984> (2018).
32. Stein, E. M. *et al.* Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia. *Blood* **130**, 722–731. <https://doi.org/10.1182/blood-2017-04-779405> (2017).
33. Lancet, J. E. *et al.* Cpx-351 (cytarabine and daunorubicin) liposome for injection versus conventional cytarabine plus daunorubicin in older patients with newly diagnosed secondary acute myeloid leukemia. *J. Clin. Oncol.* **36**, 2684–2692 (2018).
34. DiNardo, C. D. *et al.* Venetoclax combined with decitabine or azacitidine in treatment-naïve, elderly patients with acute myeloid leukemia. *Blood* **133**, 7–17. <https://doi.org/10.1182/blood-2018-08-868752> (2019).
35. Cortes, J. E. *et al.* Randomized comparison of low dose cytarabine with or without glasdegib in patients with newly diagnosed acute myeloid leukemia or high-risk myelodysplastic syndrome. *Leukemia* **33**, 379–389. <https://doi.org/10.1038/s41375-018-0312-9> (2019).

Acknowledgements

We thank Prof. Philippe Bounoux for helpful scientific discussions. We thank Mrs. Boisdrion-Celle from the *Centre Paul Papin* (Angers) for performing the PK analyses. We also thank the *Plate-Forme Lipides-Arômes* (INRA, Dijon) for performing the PUFA measurements. *The FILO Study team* We thank Ariane Mineur, Delphine Nollet, and Roselyne Delepine for diligent project management, ForDrug Consulting for pharmacovigilance, and the FILO CRAs for careful data monitoring.

Author contributions

E.G., M.C.B., C.R., and O.H. designed the study, A.P., M.H., P.P., M.C., J.-O.B., C.B., M.-P.G.-H., and B.L. contributed patients, N.V. performed pharmacovigilance comparisons, P.B. performed the statistical design and analyses, D.T. and F.D. performed PK analyses, and F.P. performed pharmacodynamic experiments on blood samples. All authors reviewed the manuscript and approved the final version.

Funding

This study was made possible by funding from the *Fondation Liliane Bettencourt*, *Force Hemato* foundation, *Association Laurette Fugain*, Fresenius Kabi, Merck-Sharp-Dohme, and Chugai. The manuscript was reviewed and commented by Fresenius Kabi GMBH.

Competing interests

EG received honoraria from Fresenius Kabi. All other authors declare no competing interests relevant for this publication.

Additional information

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1038/s41598-022-13626-y>.

Correspondence and requests for materials should be addressed to E.G. or O.H.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

© The Author(s) 2022