

Supplementary File

Modern management of anthracycline-induced cardiotoxicity in lymphoma patients: low occurrence of cardiotoxicity with comprehensive assessment and tailored substitution by non-pegylated liposomal doxorubicin

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SUPPLEMENTARY METHODS

CARDIAC ASSESSMENT

Echocardiographic cardiotoxicity was defined as a significant drop in LVEF as in Swain et al. [1] (> 10% to a final value less than 50%; > 20%; or drop to a final value > 45%, irrespective of the initial value). Baseline and final (1 year after the end of treatment) echocardiographic evaluations were done using the Vivid 9 system (GE Healthcare, Little Chalfont, UK)[1]; performed analysis included: measurement of LVEF (Simpson biplane method), measurement of global strain rate with speckle-tracking 2D-strain imaging and of systolic myocardial velocity (Sa) at the lateral mitral annulus with tissue Doppler imaging (TDI) [2].

Other data were collected within a telemedicine (TM) system, which was developed as an electronic platform for cardiology consultations. TM assessments were performed at least every 100 mg/m² of doxorubicin cumulative dose and consisted of brief history and physical examination, ECG and echocardiographic evaluation using a portable device (VScan, GE Healthcare, Little Chalfont, UK). The TM software was developed by Telemedware (Jesi, Italy). The front end TM assessment was performed by a hematologist with expertise in cardiac ultrasonography; the back end TM report was created by one expert cardiologist participating to the study. TnI measurements were performed before, 1h and 24-72h after each chemotherapy cycle (Advia Centaur, Siemens Healthcare). The monitoring schedule in a typical 6-cycle chemotherapy treatment is depicted in Fig. S1.

PLANNED TREATMENTS

Dose reductions for other drugs were applied at baseline according to age and comorbidities and subsequently according to toxicity. Prophylaxis for *Pneumocystis Jiroveci* was administered concomitantly to all CHOP-like regimens, but not to ABVD. Granulocyte-colony-stimulating factors for febrile neutropenia were administered as primary prophylaxis in all patients older than 65 years undergoing CHOP-like regimens repeated every 21 days; or in all patients undergoing CHOP-like regimens repeated every 14 days; as secondary prophylaxis in younger patients treated with CHOP-like regimens repeated every 21 days. In ABVD-treated patients, G-CSF was not routinely administered.

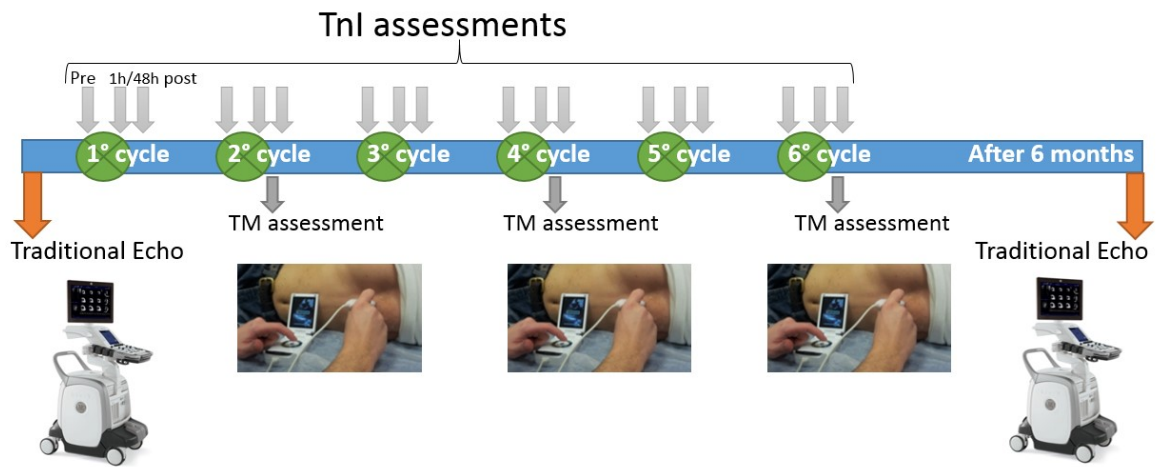
STATISTICAL ANALYSES

Descriptive statistics are reported for all the variables categorized according to type of AC used (DOX or NPLD). Binary outcomes (e.g. occurrence of cardiotoxicity, occurrence of other echocardiographic alterations, rises of TnI above pre-specified cut-offs) and continuous outcomes (e.g. change in LVEF,

change in other echocardiographic parameters, change in biomarkers values) are reported for the entire cohort and separately according to type of AC used (DOX or NPLD). The rates and proportions were compared using chi-square or Fisher's exact test. Continuous and discrete variables were compared using Student t-test or Mann-Whitney test. The distribution of time-dependent variables (e.g. overall survival) was estimated using the Kaplan-Meier product limit method. The univariate assessment for the significative time-dependent covariates was carried out with the log-rank test.

SUPPLEMENTARY FIGURES

Figure S1: Monitoring schedule in a 6-cycle chemotherapy treatment



SUPPLEMENTARY TABLES

TABLE S1: Treatment protocols

Protocol	Reference
R-CHOP21	Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, Morel P, Van Den Neste E, Salles G, Gaulard P, Reyes F, Lederlin P, Gisselbrecht C. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. <i>N Engl J Med.</i> 2002 Jan 24;346(4):235-42.
R-COMP21	Rigacci L, Mappa S, Nassi L, Alterini R, Carrai V, Bernardi F, Bosi A. Liposome-encapsulated doxorubicin in combination with cyclophosphamide, vincristine, prednisone and rituximab in patients with lymphoma and concurrent cardiac diseases or pre-treated with anthracyclines. <i>Hematol Oncol.</i> 2007 Dec;25(4):198-203.
R-CHOP14	Modified from: Wunderlich A, Kloess M, Reiser M, Rudolph C, Truemper L, Bittner S, Schmalenberg H, Schmits R, Pfreundschuh M, Loeffler M; German High-Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL). Practicability and acute haematological toxicity of 2- and 3-weekly CHOP and CHOEP chemotherapy for aggressive non-Hodgkin's lymphoma: results from the NHL-B trial of the German High-Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL). <i>Ann Oncol.</i> 2003 Jun;14(6):881-93.
R-COMP14	Modified from: Wunderlich A, Kloess M, Reiser M, Rudolph C, Truemper L, Bittner S, Schmalenberg H, Schmits R, Pfreundschuh M, Loeffler M; German High-Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL). Practicability and acute haematological toxicity of 2- and 3-weekly CHOP and CHOEP chemotherapy for aggressive non-Hodgkin's lymphoma: results from the NHL-B trial of the German High-Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL). <i>Ann Oncol.</i> 2003 Jun;14(6):881-93.
Obinotuzumab-CHOP21	GALLIUM protocol (Roch) - A Multicentre, Phase III, Open Label, Randomized Study in Previously Untreated Patients With Advanced Indolent Non-Hodgkin's Lymphoma Evaluating the Benefit of GA101 (RO5072759) + Chemotherapy Compared to Rituximab + Chemotherapy Followed by GA101 or Rituximab Maintenance Therapy in Responders.
COMEP-21	Modified from: Wunderlich A, Kloess M, Reiser M, Rudolph C, Truemper L, Bittner S, Schmalenberg H, Schmits R, Pfreundschuh M, Loeffler M; German High-Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL). Practicability and acute haematological toxicity of 2- and 3-weekly CHOP and CHOEP chemotherapy for aggressive non-Hodgkin's lymphoma: results from the NHL-B trial of the German High-Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL). <i>Ann Oncol.</i> 2003 Jun;14(6):881-93.

ABVD	Santoro A, Bonadonna G. Prolonged disease-free survival in MOPP-resistant Hodgkin's disease after treatment with adriamycin, bleomycin, vinblastine and dacarbazine (ABVD). Cancer Chemother Pharmacol. 1979;2(2):101-5.
MBVD	FIL protocol HD0803 - Multicenter phase II study in elderly patients with MBVD and / or heart disease with Hodgkin's disease (HD).

TABLE S2: Details of cardiac deaths

UPN 27	75-year-old male patient with severe chronic obstructive pulmonary disease and chronic cor pulmonale (oxygen saturation 89% at baseline) died 15 months after completing chemotherapy for DLBCL (R-COMP) because of the worsening of right heart failure.
UPN 42	49-year-old male with prosthetic aortic valve (he had underwent mediastinal radiotherapy 30 years before for malignant histiocytosis), achieved PR after 6 R-COMP cycles for high-risk DLBCL; while attaining mobilization for autologous transplantation, he had sudden death (likely due to myocardial infarction facilitated by leukocytosis).
UPN 65	67-year-old female patient with multiple cardiovascular comorbidities (2 previous strokes, previous myocardial infarction) after the 1st cycle with R-COMP for follicular lymphoma was hospitalized because of fever and dyspnea; she had several complications (new stroke) and died one month later because of heart failure (likely resulting from a new myocardial infarction)

TABLE S3: Details of patients with cardiotoxicity

UPN 11	20-year-old female patient without cardiac risk factors who had been treated for HD with ABVD followed by autologous transplantation because of resistant disease; at one follow-up visit she had a 14% absolute LVEF reduction (from 61% to 47%); she also had mild sinus tachycardia (105 bpm). Treatment was instituted with low doses of valsartan and bisoprolol, which were not tolerated due to hypotension; she was started on ivabradine and monitored monthly; 3 months after, the LVEF and the other cardiac abnormalities had completely recovered; 3 months after, ivabradine was stopped.
UPN 102	51-year-old female patient without cardiac risk factors who had been treated for DLBCL with 6 cycles of R-CHOP; 3 months after completing treatment, at one follow-up visit she had a 12% absolute LVEF reduction (from 58% to 46%); she reported mild dyspnea. She was started on low doses of bisoprolol, and monitored monthly; 3 months after, the LVEF and the other cardiac abnormalities had completely recovered.

TABLE S4: Details of patients with asymptomatic acute coronary syndrome, detected by the telemedicine system

UPN 22	76-year-old male with hypertension, hyperlipidemia and history of CAD and previous endoarterectomy, who underwent treatment with R-COMP for MCL. At the routine telemedicine evaluation before the 3rd chemotherapy cycle, he presented with diffuse T-wave inversion and a mild Tnl rise (0.09 ng/ml). He underwent coronary angiography which disclosed a severe stenosis of the left anterior descending artery which required percutaneous transluminal coronary angioplasty (PTCA) and positioning of a bare metal stent (BMS). After this intervention, the patient was able to complete the planned chemotherapy treatment.
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UPNN 25	67-year-old male with atrial fibrillation, diabetes mellitus, hyperlipidemia, hypertension which underwent treatment with MBVD for HD. Tnl measurements after the 1st MBVD cycle showed a marked increase (up to 2 ng/ml). He underwent coronary angiography which disclosed a severe stenosis of the left circumflex artery which was treated with PTCA and positioning of a BMS. After this intervention, the patient was able to complete the planned chemotherapy treatment.
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REFERENCES

1. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. *Cancer* 2003; 97(11): 2869-2879.
2. Gardin JM, Adams DB, Douglas PS, Feigenbaum H, Forst DH, Fraser AG, Grayburn PA, Katz AS, Keller AM, Kerber RE, Khandheria BK, Klein AL, Lang RM, Pierard LA, Quinones MA, Schnittger I; American Society of Echocardiography. Recommendations for a standardized report for adult transthoracic echocardiography: a report from the American Society of Echocardiography's Nomenclature and Standards Committee and Task Force for a Standardized Echocardiography Report. *J Am Soc Echocardiogr.* 2002 Mar;15(3):275-90. PubMed PMID: 11875394.
3. Dandel, M., Lehmkuhl, H., Knosalla, C., Suramelashvili, N., & Hetzer, R. (2009). Strain and strain rate imaging by echocardiography—basic concepts and clinical applicability. *Current cardiology reviews*, 5(2), 133.