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*IS THE ALL-ORAL METRONOMIC DEVEC SCHEDULE BETTER THAN INTRAVENOUS CHEMOTHERAPY PROTOCOLS IN ELDERLY WITH PERIPHERAL T-CELL LYMPHOMA?

M Christina Cox 1,2, Marta Banchi 3, Sabrina Pelliccia 1, Arianna di Napoli 4, Luigi Marcheselli5, Caterina Patti 6, Paola Anticoli Borza7, Roberta Battistini 8, Ahalya Sivashangar 2 , Francesca Di Gregorio 9, Paola Orlandi 3, Guido Bocci 3

1 Haematology Unit AOS Sant'Andrea, Rome Italy & [2]Haematology Department King's College Hospital NHS Trust, 3 Dept. of Clinical and Experimental Medicine, University of Pisa, Italy; 4 Pathology Unit, Department of Clinical and Experimental Medicine Sapienza University, Rome, Italy, 5 Fondazione Italiana Linfomiltaly; 6 Hematology Unit, '0spedale V. Cervello, Palermo, Italy, 7Hematology Unit, A.O. San Giovanni Addolorata, Rome, Italy, 8 Hematology Unit, AO San Camillo Forlanini, Rome, Italy; 9 Radiology Unit, AOS Sant'Andrea , Rome Italy,

NHS King's College Hospital NHS Foundation Trust

SISTEMA SANITARIO REGIONALE AZIENDA OSPEDALIERO-UNIVERSITARIA SANT'ANDREA

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INTRODUCTION

Peripheral T-cell lymphomas (PTCL) are rare and heterogeneous entities, with poor prognosis[1]. PTCL not-otherwise-specified (PTCL-NOS), is the most common subtype: the median overall (OS) and the progression-free survivals (PFS) were 20 and 10 months, respectively in Registry data from the T-cell project[2] . In older patients, not eligible for upfront high-dose chemotherapy , the median PFS after 1st line therapy was only 6.7 months, while following 2nd line the median PFS and OS were only 3.1 and 5.5 months, respectively.[3]

Presently, there is no standard therapy for elderly naïve and RR-PTCL (RR-PTCL): most patients become chemo-refractory and lack effective salvage regimens . Indeed, targeted drugs such as brentuximab, pralatrexate, histone deacetylase inhibitors, demethylating agents and various tyrosine-kinase inhibitors have already shown promising efficacy in PTCL, while active combinations, are paving their way . However, effective and less toxic treatment are still eagerly needed.

Metronomic chemotherapy (mCHEMO), is a promising therapeutic approach in solid tumours, but has rarely been experimented, in aggressive lymphomas [Coleman & Ruan et al] . mCHEMO can be defined as a regular administration of chemotherapy that is able to sustain low, prolonged, and active plasma levels of drugs causing a favourable tolerability[4]. mCHEMO is now considered a multi-targeted therapy which may act on the anti-angiogenic and immune mediated effects that lead to tumour dormancy. More recently, also the direct impact on cancer cell proliferation has been demonstrated.

Recently, the all-oral metronomic schedule DEVEC [Deltacortene® (prednisone), etoposide, vinorelbine, cyclophosphamide] was shown to induce sustained remission in diffuse-large-B-cell lymphoma (DLBCL) patients.[5]

AIM

The aim of the present study was to:

- explore the all-oral DEVEC metronomic schedule in elderly, vulnerable PTCL patients, unfit for intravenous chemotherapy schedules
- To assess the in vitro activity of Vinorelbine and Etoposide at metronomic doses in T-cell lymphoma cell lines

METHOD

STUDY & THERAPEUTIC SCHEDULE

Four Italian clinical centres prospectively collected data on PTCL patients treated with the DEVEC schedule (Ethical Approvaln°4640), between 2013 and 2018. All the data were retrieved as of 10thJanuary 2020. DEVEC foresee an induction and a deescalated maintenance phase, both consisting of six cycles of 28-days each . DEVEC was previously described[5] and is shown in figure 1 . In subjects achieving less than complete response (CR), maintenance cycles were delivered alternating: 1) cyclophosphamide (CTX) 50 mg for 14 days/etoposide (ETO) 50 mg for 7 days and 2) CTX 50 mg for 14 days/vinorelbine (VNR) 30 mg thrice a week 3weekson/1 week off, until progression or excessive toxicity. Adverse drug reactions were recorded based on CATCAE v4.03.

PATIENTS SELECTION: 1) treatment-naïve, frail by CGA [10] and ≥65y, or unfit and ≥85y; or 2) R/R ≥55y, recognized not fitting for transplant . RESTAGING: An interim restaging was carried out between the 2nd and 3rd induction-cycles and on completion of the induction phase by FDG positron-emission CT-scan (CT-PET) and evaluated basing on the revised Cheson's criteria (2007).

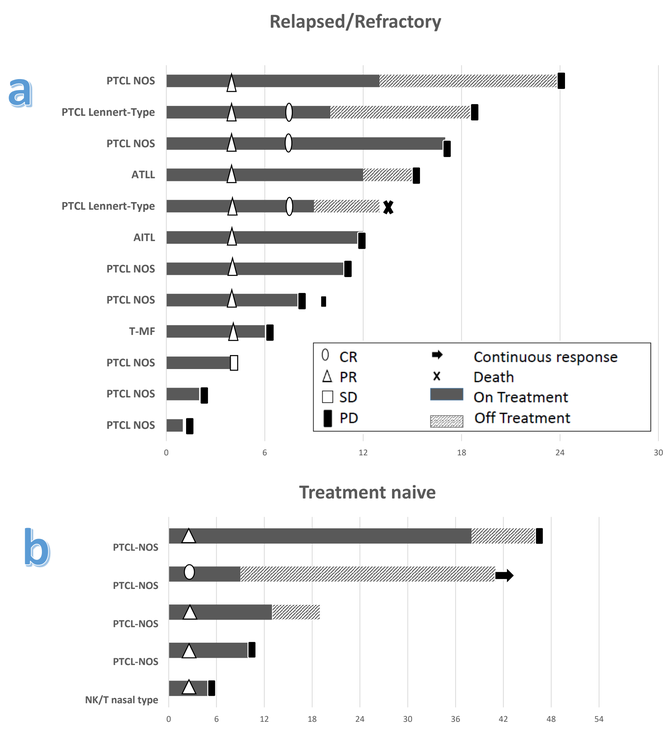
IN VITRO EXPERIMENTS: The human PTCL cell line HH (ATCC® CRL-2105™) (2 x 10^4 cells/well) were cultured into 24-well sterile plastic plates and allowed to replicate overnight. Cells were treated with VNR (0.001 nM-10 nM) and ETO (0.025 nM-100 nM), or with vehicle alone for 144 h, as previously described [12][8]. VNR or ETO were added every 48 h or 24 h, respectively, to mimic the clinical schedules, such as the thrice a week metronomic VNR treatment or the daily metronomic ETO administration (Figure 1A). At the end of the treatment, the viable cells were counted with a hemocytometer. Cell viability was assessed by trypan blue dye exclusion. The number of treated cells was expressed as a percentage of control ones (vehicle alone). The drug concentrations that decreased cell proliferation by 50% (IC_{50}) compared to vehicle-treated cells were calculated by a nonlinear regression fit of the obtained mean values. Furthermore, the concomitant combination of VNR and ETO was performed at different concentrations with a fixed molar ratio of 1:100, respectively. The synergistic, additive and antagonistic effect of the drug combination was mapped with the Loewe additivity model, using the Combenefit software. All experiments were repeated, independently, three times with at least nine samples for each concentration (v.2.021;https://sourceforge.net/projects/combenefit/files/Combenefit%202.02%20WIN_64%20%28PREFERRED%29, last access 04-07-2020)..

RESULTS

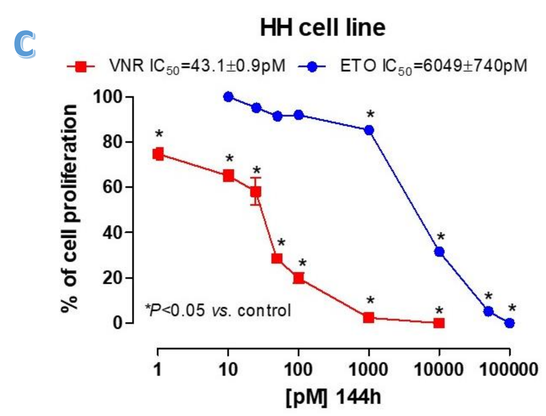
Patients' features

	Naive	Relapsed/Refractory
Median Age (range)	83 years (70-87)	71,5 years (56-85)
Male sex	4/5 (80%)	6/12 (50%)
DIAGNOSIS		
PTCL NOS	4	7
PTCL NOS Lennert type		2
AITL		1
NK/T nasal type	1	
ATLL/nodal		1
tMF		1
Stage III-IV	5/5	11/12
IPI 3-5	5/5 (100%)	9/12
PIT 3-4	5/5 (100%)	8/12
Previous Chemo(median,range)	-	1-3(1)
DEVEC cycles (median, range)	10 (7-38)	8,5 (1-13)
ORR	4/5 (80%)	8/12(66%)
CR	1/5 (20%)	3/12 (25%)

Figures



Swimmer-plot of Relapsed/Refractory and Treatment-naïve PTCL patients following DEVEC.



Antiproliferative activity of metronomic vinorelbine (144 h) and metronomic etoposide (144 h) on HH cells. *Symbols and bars*, mean values ± SEM. *, *P*<0.05 *vs*. control

In vitro experiments showed that both metronomic VNR and daily metronomic ETO caused a significant, direct, concentration-dependent inhibitory activity on HH cell proliferation with an experimental IC_{50} of 43.1±0.9 pM and 6.05±0.74 nM (Figure 1c), respectively. Computational quantification of the drug combination responses, showed that the combination of VNR with ETO in HH cells was highly synergistic using the Loewe additivity model.

From September 2012 to August 2018, 17 subjects started the DEVEC schedule (Table) . Haematological treatment-related-adverse-events (TRAE) were recorded in 8/17 patients, the most frequent was G3 neutropenia in 6/17 (35%). Four G4 neutropenia lasting for more than 6 days, occurred in 3/17 (17.6%) patients. Five non-Haematological TRAE of grade ≥3 were recorded in 4/17 patients (23.5%): they were all infective. No treatment related deaths occurred. The median follow-up, was 45 months (range=14-72). At the time of analysis 16/17 (94%) patients died: 15/17 (88%) for disease progression and 2/17 (12%) for non-TRAE. Tumour shrinkage was recorded in 5/5 (100%), naïve (95%CI=55-100%) and in 9/12 (75%), RR (95%CI=43-95%) (Figure1E, F). The ORR was 80% and 58% in naïve and RR, respectively. CR was observed in 1/5 (20%) naive and 3/12 (25%) RR, respectively. Median PFS and OS for naïve was 20 (CI 95%= 0-43) and 46 months, respectively. While in RR the OS was 13 months (CI 95%= 11.3-14.6) and the median PFS was 11 months (CI 95%=4.2-17.8). Worthy of note the median PFS of the RR subset, to the treatment done before the DEVEC had been only 5 months (CI 95%= 3.3-6.7).

CONCLUSIONS

All-oral metronomic DEVEC chemotherapy resulted in an objective response in most of naïve and RR patients, allowing a durable remission. Worthy of note the RR group had after DEVEC a mPFS longer than the mPFS achieved after previous intravenous regimens.

In this difficult-to-treat NHL subset, DEVEC is an active and convenient regimen. In fact, it allows to drastically reduce the admission to hospital of elderly subjects, which in the COVID pandemic has become a priority.

Our experimental data, clearly show that both VNR and ETO, included in the DEVEC schedule, significantly affected the PTCL cell proliferation. Both given *in vitro* metronomically were active at very low concentrations (pM and nM, respectively). Furthermore, their concomitant combination revealed to be highly synergistic in HH cells

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CONTACT INFORMATION

M Christina Cox,
Haematology Dept. King's College Hospital
Christina.cox2@nhs.net