Early Phase I Results for 4-Demethyl-4-cholesteryloxypenclomedine [DM-CHOC-PEN] as Therapy in Adolescent and Young Adult (AYA) Subjects with Advanced Malignancies

L.R. Morgan[1,*], R.S. Weiner[2], M.L. Ware[3], M. Bhandari[4], T. Mahmood[5] and P. Friedlander[6]

[1]*DEKK-TEC, Inc., New Orleans, LA, USA*

[2]*Tulane University Medical Center, New Orleans, LA, USA*

[3]*Ochsner Medical Center, New Orleans, LA, USA*

[4]*The Christ Hospital, Cincinnati, OH, USA*

[5]*Detroit Clinical Research Centers, Owosso & Lansing, MI, USA*

[6]*Mount Sinai Medical Center, New York, NY, USA*

Abstract: 4-Demethyl-4-cholesteryloxycarbonylpenclomedine (DM-CHOC-PEN) is a poly-chlorinated pyridine carbonate with a MOA *via bis*-alkylation of DNA @ N^7-guanine and N^4-cytosine that has completed adult clinical Phase I and II trials in individuals with malignancies involving the CNS. We report here objective clinical observations seen in a clinical Phase I DM-CHOC-PEN trial with AYA subjects that have cancer (some of which had CNS involvement).

Subjects & Methods: DM-CHOC-PEN was administered as a single 3-hr IV infusion once every 21 days in escalating doses from 50 – 98.7 mg/m^2 to individuals (aged 15-39 years of age) with advanced malignancies.

Results: Twelve (12) AYA individuals have been treated to date (with or without CNS involvement). The drug was well tolerated with fatigue (17%) being the most common adverse effect. No neuro/cognitive, liver dysfunction, hematological, cardiac, renal or GI toxicities were observed. Pharmacokinetic profiling revealed higher AUCs for all dose levels (50-98.7 mg/m^2) than had been seen previously in adults. Three (3) AYA individuals treated (1 each with NSCLC, ALL, and astrocytoma involving the CNS) have responded with CR/PR (RECIST 1.1), improved QOL/PFS (Kaplan-Meier) and OS from 8 to 35+ mos.

Conclusion: DM-CHOC-PEN is safe in doses of 50-98.7 mg/m^2 and produced objective responses with improved OS and manageable toxicities in AYA individuals with malignancies involving the CNS. Complete data on subject responses and observed toxicities will be presented. The data support a 3-stage mechanism for tumor cytotoxicity: entry into the CNS and into the tumor *via* reversible binding to RBC membranes; then transported into cancer cells with L-glutamine; and *bis*-alkylation as described above.

Keywords: Cancer, central nervous system, metastatic, primary, DM-CHOC-PEN, non-neurotoxicity.

INTRODUCTION

Almost 700,000 individuals are living in the US with malignancies involving the central (CNS) or spinal nervous system (SNS) [1]. Nearly 15% of these tumors occur in adolescents or young adults (AYA), aged 15-39 years of age [2]. It is predicted that 10,617 AYA individuals will be diagnosed with brain or CNS tumors resulting in 434 deaths this year in the US [1]. AYA individuals with histories of cancer, who appeared to have 'beaten the odds' are now developing recurrent cancers involving the CNS years after remission in increasing rates [2, 3]. Primary brain tumors (glioblastoma (GBM), etc.) and metastatic cancers – *melanoma, leukemia and sarcomas* involving the CNS are the most common types of malignancies reported in AYA population [4-7].

Innovation and Significance

4-Demethyl-4-cholesteryloxypenclomedine [DM-CHOC-PEN] (Figure **1**) is a polychlorinated pyridine carbonate developed at DEKK-TEC that is lipophilic, electrically neutral, crosses the blood brain barrier (BBB) and is non-neurotoxic [8, 9]. The drug has been evaluated in adult Phase I and II clinical trials in individuals with advanced malignancies involving the CNS and SNS with objective responses and has improved over-all survival and improved performance status lasting up to 5-years (IND 68,876; NCT02889445) [9-11].

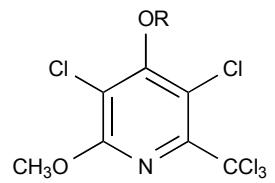

Figure 1: Penclomedine analogs – PEN (R=CH_3); DM-PEN (R=H); DM-CHOC-PEN (R= CO_2-cholesteryl).

*Address correspondence to this author at the DEKK-TEC, Inc., 725 Topaz Street, New Orleans, LA 70124, USA; Tel: 504-583-6135;
E-mail: lrm1579@aol.com

ISSN: 1929-2260 / E-ISSN: 1929-2279/18

A Phase I clinical trial with DM-CHOC-PEN in AYA individuals with advanced malignancies (+/- CNS involvement) is in progress and early results are reported here (IND 68,876).

SUBJECTS AND METHODS

The current Phase I AYA protocol involved enrollments of 3-indivdual cohorts beginning with 50 mg/m^2 and subsequent groups treated at 40% increments in escalating dosing levels. DM-CHOC-PEN was administered intravenously once every 21-days. Complete hematology, chemistry, and urine profiles, and electrocardiograms were obtained before and after treatments. Pharmacokinetic profiles were obtained before and at timed intervals after treatments.

RESULTS

The maximum administered dose (MAD) as 98.7 mg/m^2 with minimal nausea, observed in 1-individual treated at the 75 mg/m^2 a dose. The dose levels that have been administered to individuals were - 50, 75, and 97.8 mg/m^2.

Twelve (12) individuals of whom ten (10) had malignancies involving the CNS have been treated to date in the Phase I trial. All had failed previous therapies at least 6-8 weeks prior to enrollment. Eligibility criteria were: a Zubrod PS score of 0-2, adequate renal/hepatic/hematological functions. Individuals with liver metastasis were eligible, however, liver functions were <1.5 x ULN. All individuals requiring anticoagulation with warfarin or equivalent were excluded [7].

Table **1** reviews all cohorts that have been enrolled, treated and monitored in the trial to date.

Clinical Toxicity

Hematology, complete chemistry and neurological profiles have remained stable in the treated individuals. A complete cognitive/behavioral examination was performed before, during and after treatments during weekly visits. No mental/cognitive behavioral toxicities have been noted.

Pharmacokinetic (PK) Profile

For AYA individuals, areas under the curves (AUC) were parallel for all dose levels 50-98.7 mg/m^2 and C_{max} occurred ~ 150 hours [7, 8]. The metabolite, DM-PEN had no activity in published NCI trials and was discontinued from clinical testing [10]. Figure **2** displays the comparative pharmacokinetics (C x T) for DM-CHOC-PEN in plasma from 30, 50 and 60 y/o individuals with cancer involving the CNS. AUCs were higher at all AYA doses then were seen in adults [8, 10]. The HPLC analyses utilized to measure DM-CHOC-PEN is reviewed in the pre-clinical and Phase I adult clinical reports [9,10]

Preclinical PK modeling revealed that the drug enters a central compartment (cpt) and is then released into the peripheral circulation with a $T_{1/2\ \alpha}$ of ~ 28 hrs and an area under the curve ($AUC_{o\text{-}t}$) = ~11 mg·h/L, for both adults and AYA at 75 mg/m^2 dose level [10]. The C_{max} for AYA individuals was higher *vs*. those reported for adults (Figure **2**).

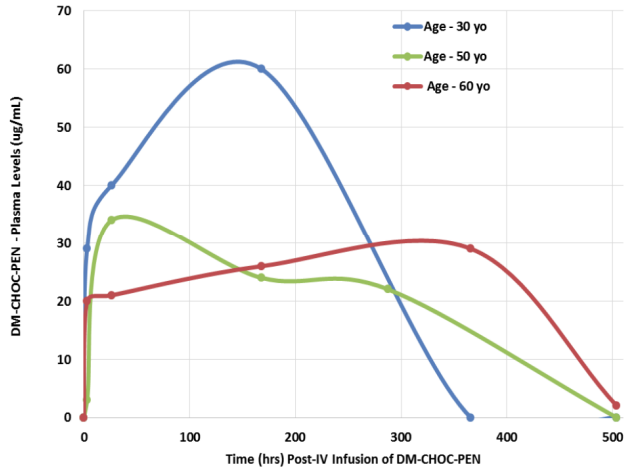

Figure 2: Post IV DM-CHOC-PEN – 75 mg/m^2.

DM-CHOC-PEN was detected after 3 to 15 days bound to RBCs (50%) (10). DM-CHOC-PEN is released from RBCs, with neither RBC destruction nor reduced RBC values noted (no anemia). DM-CHOC-PEN was also detected in the urine (C_{max}=17.5 µg/mL @ day 15) and observed to be present in the blood until day 21 in several individuals in the 98.7 mg/m^2 cohort [10].

DISCUSSION

To date, twelve (12) individuals have been treated in the present Phase I clinical trial; ten (10) had cancer involving the CNS.

Two of the AYA subjects: one (1) with metastatic (non-small cell lung cancers, NSCLC) involving the CNS and one (1) with a primary CNS astrocytoma have responded well and are now with no evidence of disease (NED) – 35+ and 36+ mos., resp., after 4-5 treatments.

Table **1** reviews these AYA subjects, their doses (39, 55, or 97.8 mg/m^2), responses and toxicities. Several subjects received more than 1-dose level of drug. All individuals had advanced, chemo-resistant stage IV cancer - melanoma, NSCLC, breast, acute lymphocytic leukemia, oligodendroglioma and astrocytoma [9, 10].

Enrollment criteria for the individuals in the trial required a Zubrod PS score of 0-2, adequate renal/hepatic/hematological functions, and stable mental/neurological systems. Individuals with liver metastasis were eligible providing the hepatic functions were < 1.5 x ULN. Individuals requiring full-dose anticoagulation were excluded.

The current Phase I AYA protocol had received full approval by the FDA, CTEP, IRBs and permits enrollment of individuals at escalating doses of 50, 75, and 97.8 mg/m^2 once every 21 days (14). New subjects could be added to a higher dose cohort providing one or more subjects receive 2-cycles of the drug at a given dose level (to avoid accumulative toxicity). When a severe limiting toxicity (SLT) was observed, the study will be expanded to 5-6 subjects at that dose cohort. Two (2) SLTs at the same dose levels will define the MAD (maximum administered dose). At least 5-subjects will be treated at the dose level below the MAD, and, if safe, this level will be the maximum tolerated dose (MTD) and the starting dose for future AYA Phase II trials.

To date no SLTs in the AYA aged group have been observed; however, no individuals have been treated in the Phase I trial that had pre-existing hepatic or other chronic non-malignant illnesses.

The clinical toxicity observed for DM-CHOC-PEN in the adult Phase I/II trials has been primarily hepatic – elevated bilirubin [9, 10]. Elevations in lipid profiles were observed in the rat studies, thus the human studies were watched closely for lipid profile abnormalities. Transient hypercholesteremia and hyperlipidemia from the vehicle plus metabolism of DM-CHOC-PEN to DM-PEN and cholesterol have been seen in the adult Phase I trial, but not in the AYA study [10]. The lipid profiles (cholesterol and triglycerides) for the subjects were erratic during the 3-h IV infusion period (2^o to the lipid emulsion vehicle and release of cholesterol), however, they returned to pre-treatment values after 24 hours. Triglycerides were the most significantly affected [9]. Hepatic imaging failed to demonstrate hepatic cysts or changes secondary to DM-CHOC-PEN in clinical trials [9, 10].

Complete chemistry and hematology profiles have remained stable, plus, cognitive/behavioral examinations performed before, during and after each treatment, and weekly have revealed no abnormalities [9, 10]. The mental status exam satisfied all IRB requirements [7].

The drug's acceptability and responses noted in an AYA aged population with cancer that have been treated with DM-CHOC-PEN is encouraging. Moreover, AYA subjects with cancer have become a major interest, since other than having cancer, they are generally heathier than older subjects and may

Table 1: AYA Subjects with Advanced Cancers Treated with IV DM-CHOC-PEN to Date

Cancer Type (#)	Age/Sex	Dose (mg/m^2)	Responders w/ CNS (#)	OS (w/CNS) (mos)	Toxicity
Breast (2)	33/F 29/F	50 50	1 0	12 3	None None
Pontine glioma (1)	22/M	50	Too soon	1+	None
Melanoma (1)	39/F	75	0	2	None
Gastric (1)	19/F	75	Too soon	1+	None
GBM (2)	34/F 34/F	75 98.7	NR NR	4 2	Nausea*** None
ALL (1) NHL (1)	39/M 28/F*	98.7 98.7	CR NR	8** 6+	None None
Oligoastrocytoma (1)	39/M	98.7	NR	3	None
Astrocytoma (1)	31/M	98.7	1	35+	None
Lung cancer (NSCLC) (1)	39/F	98.7	1	35+	None

*No CNS disease & no responses; **CNS – CR, w/ peripheral progression; ***Gr-2 nausea.

tolerate the drug differently. The latter may be an explanation for the PK differences seen for AYA *vs.* older subjects in Figure **2**; however the group is still at risk for toxicity from DM-CHOC-PEN.

Plus, since AYA individuals with advanced malignancies are not commonly enrolled in early clinical trials, survival information for this group is not available (only incidence and death), thus this age group may be isolated from potential maximum care [13, 14].

ACKNOWLEDGEMENTS

NCI/SBIR grants-R43/44CA132257; R43CA203351.

REFERENCES

[1] Siegel RL, Miller KD, Jemal A. Cancer Statistics. CA Cancer J Clin 2017; 67: 7-30. https://doi.org/10.3322/caac.21387

[2] Wilson E. Brain tumors affect adolescents and young adults differently. Hem Onc Today 2016; 8-9.

[3] Termini J, Neman J, Jandial R. Role of the neural niche in brain metastatic. Cancer Res 2014; 74: 4011-4015. https://doi.org/10.1158/0008-5472.CAN-14-1226

[4] Franklin A. A Growing identity for adolescent and young adult oncology. Oncology Times 2016; 38: 8-10. https://doi.org/10.1097/01.COT.0000508317.51300.6e

[5] Hayes-Lattin. Integrating AYA oncology care into the worlds of pediatric and adult oncology care to improve cancer outcomes. The ASCO Post 2016; 10: 82-83.

[6] Pemmaraju N. Adolescent & young adults with chronic myeloid leukemia. Oncology Times 2017; 39(Issue 10): 25-26. https://doi.org/10.1097/01.COT.0000520172.33444.4e

[7] Weiner RS, Ware ML, Bhandari M, Mahmood T, Friedlander P, Morgan LR. The tolerance and safety of 4-demethyl-4-cholesteryloxycarbonylpenclomedine (DM-CHOC-PEN) in adolescent and young adult (AYA) subjects with advanced malignancies. J Transl Sci 2017; 3: 1-4.

[8] Morgan LR, Struck RF, Waud WR, Jursic BS, Serota D, Papagiannis C, Rodgers AH. Carbonate and carbamate derivatives of 4-demethylpenclomedine as novel anticancer Agents. Cancer Chemotherapy Pharmacology 2009; 64: 618-623. https://doi.org/10.1007/s00280-009-0933-9

[9] Morgan LR, Rodgers AH, Bastian G, Benes E, Waud WS, Papagiannis C, Krietlow D, Jursic E, Thompson R. Comparative preclinical pharmacology and toxicology for 4-demethyl-4-cholestryloxylcarbonylpenclomedine (DM-CHOC-PEN) – a potential neuro-alkylating agent for glioblastoma (GBM) and metastatic cancers involving the central nervous system. In: Morgan, LR, editor. Tumors of the Central Nervous System – Primary and Secondary. Rijeka: InTech; 2014; pp. 239-263.

[10] Weiner RS, Friedlander P, Gordon C, Saenger Y, Ware RL, Mahmood T, Rodgers AH, Bastian G, Urien S, Morgan LR. A phase I cancer clinical trial for 4-demethyl-4-cholesteryl-oxycarbonylpenclomedine (DM-CHOC-PEN). Proc Am Assoc Cancer Res 2014; 56: 746.

[11] Weiner RS, Friedlander P, Gordon C, Saenger Y, Ware RL, Mahmood T, Rodgers AH, Bastian G, Urien S, Bhandari M, Morgan LR, Zu J-J. Results of Phase II cancer clinical trials for 4-demethyl-4-cholesteryoxycarbonylpenclomedine (DM-CHOC-PEN). Proc Am Assoc Cancer Res 2016; 58: 236.

[12] Morgan LR, Benes E, Rodgers AH, Weiner RS, Mahmood T. Penetration of NSCLC involving the CNS *via* L-glutamine transport. 16th Int. Lung Cancer Congress 2015: Abstr. 6.

[13] Toronezos ES. Discussions on adolescent and young adult survivorship. Cancer Survivorship Symposium 2017.

[14] Doyle C. What do we still need to know about adolescent and young adult survivorship? Oncology Practice Management 2017; 34-35.

Received on 24-04-2018 Accepted on 05-05-2018 Published on 25-06-2018

DOI: http://dx.doi.org/10.6000/1929-2279.2018.07.03.2