Comparative Pharmacokinetics for 4-Demethyl-4-Cholesteryloxypenclomedine [DM-CHOC-PEN] In Adolescent and Young Adults (AYA) vs. Adult Subjects with Advanced Malignancies Involving the CNS

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Editorial

Malignancies of the central nervous systems (brain and spinal cord) occur at every age level of human life; no age group is spared the possibility of developing a primary or secondary Central Nervous System (CNS) malignancy [1]. Almost 700,000 people in the US are living with tumors in the CNS [1-3]. An additional 400,000 individuals are estimated to be living in other parts of the world with malignancies in the CNS [2]. Although the age range that is most affected by CNS malignancies are the 50 to 70s, no age range is spared [1]. It is estimated that nearly 15% of CNS tumors worldwide involve the Adolescent/Young Adult (AYA) age group, 15 years to 39 years of age [2]. It is predicted that in the US alone 10,617 AYA aged individuals will be diagnosed with CNS tumors resulting in 434 deaths this year [1].

The AYA age group of individuals with malignancies deserves special attention since they generally lack histories of comorbidities - hypertension, pulmonary, hepatic diseases, etc. and may tolerate drugs differently from older subjects. They may still be at risk, however, for toxicity with immuno/chemotherapy regimens in current use. AYA individuals with cancer also demonstrate different host biology, tumor pathophysiology and metabolize chemotherapy drugs differently than do either younger or older individuals [2,4]. Weiner et al., [5,6] presented early Phase I results and experiences with 4-demethyl-4-cholesteryl-oxypenclomedine (DM-CHOC-PEN) as treatment for cancers involving the CNS in both adults and in AYA individuals. Both the AYA and older adult subjects involved in the Phase I trials received intravenous doses 39 mg/m2, 55 mg/m2, 75 mg/m2 or 97.8 mg/m2 (DM-CHOC-PEN) administered once every 21 days). Complete responses in a variety of tumors solid as well as leukemia have demonstrated remissions lasting up to 5-years [5,6]. To date seventy-two (72) subjects both AYA and adult individuals have been treated. The AYA subjects had advanced, chemo-resistant stage IV cancer melanoma, NSCLC, breast, acute lymphocytic leukemia, oligodendroglioma and astrocytoma [5,6].

Unlike other penclomedines (e.g., PEN, NSC 338720, (Figure 1)), DM-CHOC-PEN is non-neurotoxic, lacks hematological toxicities, does not require hepatic activation, crosses the Blood Brain Barrier (BBB) and accumulates in brain tumors [6,7]. A proposed mechanism of action for DM-CHOC-PEN involves association with erythrocyte membrane surfaces, penetration of the BBB and CNS parenchyma and transportation into CNS tumors with L-glutamine, with which it shares common structural moieties [7].

The pharmacokinetic profiles for DM-CHOC-PEN in AYA vs. 50 years to 60 years adult subjects support the influence of individual comorbidity on drug metabolism; for the former vs. latter- Cmax=60.32 µg/mL; AUC=13.008±10.687 µg.h/mL and T1/2β=28.71 h. The higher Cmax, higher AUC (total drug available) and lower T1/2β (rate of degradation) values for the AYA subjects reflects a
‘healthier’ metabolic profile (lesser microsomal P450 alterations with other drugs, etc.) for the drug than exist in the older adults that were receiving other medications for associated comorbidities resulting in induced/altered hepatic metabolic activity. This difference may be present for other drugs as well and not commonly defined by age. In Figure 2, diagrams the differences in drug disposition vs. age.

Moreover, AYA subjects, especially the 15 years to 20 years olds are of major interest since they are not commonly enrolled in clinical trials and typically managed by pediatric and/or adult oncologists, rather than AYA oncology specialists that also appreciate the issues they face physical, psychosocial, emotional, sexual, spiritual, financial, dietary, etc. and able to translate knowledge to them [3,8].

A Phase II clinical trial with DM-CHOC-PEN in AYA subjects (15 years to 39 years old) with malignancies involving the CNS is in progress to validate and expand the above observations.

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References

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