Randomized Trial of Protease Inhibitor-Based Antiretroviral Therapy for Kaposi Sarcoma in Africa

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Background: Combination antiretroviral therapy (ART) — including protease inhibitor (PI)-containing regimens — has long been known to decrease lesion burden in some patients with Kaposi sarcoma (KS), but exactly which ART component/mechanism is responsible is unknown. Among the potential explanations, PIs have been speculated to have direct anti-KS effects in humans based on their anti-angiogenesis effects in vitro. We investigated the hypothesis that PI-based ART is clinically superior to PI-sparing ART for the treatment of KS in sub-Saharan Africa, a region where initial ART choice is critical given scarcity of chemotherapy.

Methodology: We enrolled ART-naïve HIV-infected adults with KS in Uganda who had no urgent indications for chemotherapy/radiotherapy. Subjects were randomized to either PI-based (lopinavir/ritonavir plus emtricitabine/tenofovir) or non-nucleoside reverse transcriptase inhibitor (NNRTI)-based ART (efavirenz plus emtricitabine/tenofovir) and observed every 4 weeks for 48 weeks for an indication for chemotherapy and overall survival. Chemotherapy was given free for those who developed an indication post-randomization.

Results: Among 224 subjects randomized (113 PI/111 NNRTI) in this completed trial, 44% were women and median pre-treatment values were: 34 years old, 119 CD4+ T-cells/mm³ and 222,323 copies plasma HIV RNA/ml. Extent of KS was heterogeneous: 7.1% had oral lesions only, 24% had ≥50 skin lesions, and 71% were T1. ART was well tolerated with only 7.1% in the PI arm and 8.1% in the NNRTI arm discontinuing their original drug class. There was no loss to follow-up from the perspective of vital status, and only 3 alive subjects were unavailable for clinical assessment at 48 weeks. A total of 36% of subjects experienced the primary composite outcome (indication for chemotherapy or death) by 48 weeks, but we found no evidence in intent-to-treat analysis for a difference between treatment groups (Fig. 1a). Likewise, for mortality alone, 18% of subjects died by 48 weeks, but we found no treatment differences (Fig. 1b).

Conclusions: Despite biological plausibility, we found no evidence that PI-containing ART was superior to NNRTI-based ART in terms of survival or need for chemotherapy amongst patients with KS who did not initially have urgent chemotherapy indications. The high incidence of subsequent indications for chemotherapy and/or death indicates that ART alone for all comers with KS in Africa is suboptimal and additional interventions are needed.