Outcomes in Kaposi sarcoma herpesvirus-associated multicentric Castleman disease patients treated with rituximab and liposomal doxorubicin (R-Dox)

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INTRODUCTION

- Kaposi Sarcoma (KS) herpesvirus-associated multicentric Castleman disease (KSHV-MCD) is a lymphoproliferative disorder commonest in the setting of HIV
- Disease manifestations are associated with increases in IL-6, KSHV-encoded viral IL-6, as well as increased IL-10[1,2]
- Rituximab improves symptoms and overall survival and decreases NHL risk in KSHV-MCD
- However, concurrent KS is common and can worsen with rituximab.
- Liposomal doxorubicin targets CD20-negative KSHV+ cells (i.e. spindle cells, plasmablasts), and is FDA approved for KS
- Rituximab combined with liposomal doxorubicin (R-Dox) is safe and effective in KSHV-MCD[3]
- Long term outcomes in KSHV-MCD with concurrent KS is unknown.

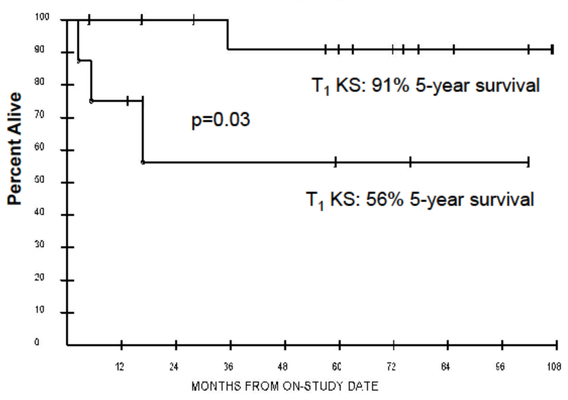
METHODS

- Patients (pts) with symptomatic KSHV-MCD were treated in a prospective study of rituximab 375mg/m^2 and liposomal doxorubicin 20mg/m^2 every 3 weeks (R-Dox) until clinical improvement[3], followed by antiviral therapy (high-dose zidovudine combined with valganciclovir or interferon-α[4]
- Pts received concurrent antiretroviral therapy for HIV
- Additional KS therapy was administered if clinically indicated
- KSHV-MCD responses were evaluated by NCI criteria, survival by Kaplan-Meier and log-rank methods.
- Baseline clinical factors were evaluated as predictors of overall survival (OS)
- Effect of R-Dox on change in clinical biomarkers evaluated by Wilcoxon signed rank test. 2-sided P-value < 0.05 considered significant.

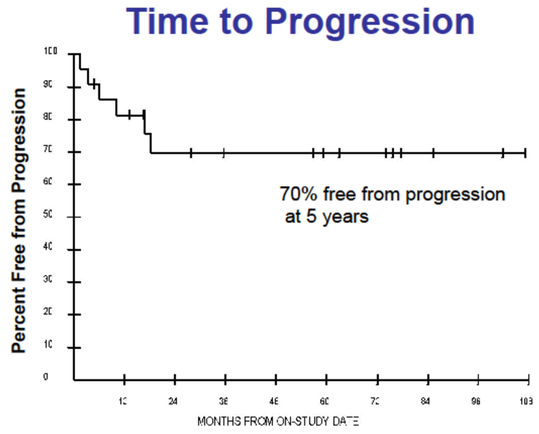
RESULTS

Baseline Patient Characteristic	Results	
Age, med (range)	43	(27-55)
CD4 (cells/uL), med (range)	255	(21-858)
HIV viral load (VL) <200 copies/mL, n(%)	17	(77.3%)
Prior KSHV-MCD therapy, n (%)	16	(72.7%)
CRP (mg/L), med (range)	81.5	(<4-210)
Hemoglobin (g/dL), med (range)	9.8	(6.8-13.2)
Platelets (K/uL), med (range)	118.5	(11-567)
Albumin (mg/dL), med (range)	2.9	(1.2-4.0)
KSHV VL (copies/10^{6}PMBC), med (range)	18,622	(0-8,780,488)
Serum Free Kappa (mg/dL), med (range)	7.4	(1.9-22.6)
Serum Free Lambda (mg/dL), med (range)	5.7	(1.8-19.8)

Overall Survival



Time to Progression



- 22 HIV+ pts enrolled, includes 17 previously published pts[3].
- 10 (45%) had KS (including 1 pulmonary KS), 4 additional had KS in lymph node only, 8 (36%) T_1 KS (high-risk KS based on lymphedema, extensive oral cavity involvement or visceral disease).
- Median number of cycles 3 (2-9).
- At end R-Dox, clinical benefit responses: complete 77%, partial 9%, stable disease 5% progressive disease 9%.
- During R-Dox, 8 had improvement in cutaneous KS, only 1 pt had mild transient worsening.
- Hemoglobin, albumin, CRP, KSHV viral load (VL), and serum free light chains improved with therapy (p<0.0001).
- With median potential 69 month follow up, 5-year estimates:
  - 70% (95% CI: 47-86%) free from KSHV-MCD progression
  - OS 79% (56- 92%).
- Baseline T_1 KS was associated with inferior OS (Figure)
- Baseline CD4 <100 cells/uL (p=0.33), hemoglobin (p=0.29), platelets (0.36), KSHV VL (p=0.93), CRP (p=1.00) and serum free light chains (K, p=0.22, L, p=0.32) were not associated with OS.

CONCLUSIONS

- R- dox is effective in KSHV-MCD, including many pts with concomitant KS
- Baseline measures of KSHV-MCD activity or CD4 count were not associated with OS
- Inferior survival was noted in the few patients with baseline advanced (T_1) KS treated with R-Dox
- Improved understanding of causes of death in patients with KS[1] is required and novel treatment approaches are needed for this population

REFERENCES

1. Uldrick TS, Wang V, O'Mahony D, *et. al.* An IL-6-related systemic inflammatory syndrome in patients co-infected with Kaposi sarcoma-associated herpesvirus and HIV but without multicentric Castleman disease. *Clin Inf Dis.* 2010 Aug 1;51(3):350-8.

2. Polizzotto MN, Uldrick TS, *et. al.* Human and viral interleukin-6 and other cytokines in Kaposi sarcoma herpesvirus-associated multicentric Castleman disease. *Blood.* 2013 Dec 19;122(26):4189-98.

3. Uldrick TS, Polizzotto MN, Aleman K, *et. al.* Rituximab plus liposomal doxorubicin in HIV-infected patients with KSHV-associated multicentric Castleman disease. *Blood.* 2014 Dec 4;124(24):3522-52.

4. Uldrick TS, Polizzotto MN, O'Mahony D, *et.al.*. High-dose zidovudine in combination with valganciclovir in the treatment of symptomatic Kaposi sarcoma-associated herpesvirus-associated multicentric Castleman disease: A pilot study of virus-activated cytotoxic therapy. *Blood.* 2011 Jun 30;117(26):6977-86.

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