INFECTIOUS AGENTS AND CANCER

MEETING ABSTRACTS Open Access

The use of high-dose azidothymidine in combination with chemotherapy upfront is an effective treatment approach for gamma-herpes virus-related non-Hodgkin's lymphomas

Ulas Darda Bayraktar[1], Eileen Bernal[1], Lisa Cabral[1], William J Harrington Jr.[1], Dirk P Dittmer[2], Juan Carlos Ramos[1*]

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Background

Azidothymidine (AZT), a thymidine analogue, is an excellent substrate for gamma-herpes virus thymidine kinases (TKs). Our group previously demonstrated that AZT alone can inhibit NF-κB and disrupt EBV latency in primary low-passage Type I latency EBV+ Burkitt lines. The addition of hydroxyurea, which increases the intracellular levels of AZT monophosphate, synergized with AZT in Type III latency EBV+ immunoblastic lymphoma cell lines. The use of AZT in targeting gamma-herpes virus lymphomas is an attractive concept given that this drug is preferentially phosphorylated by EBV and HHV-8 TKs as compared to non-thymidine nucleoside analogues. The drugs methotrexate (MTX) and doxorubicin (DOX) also induce lytic expression of gamma-herpes viruses. MTX inhibits thymidylate synthase, thus blocking de novo synthesis of dTMP and increasing the likelihood of AZT incorporation into DNA. We have found that the combination of high-dose AZT with MTX, used alone or with alternating standard chemotherapy, can result in dramatic

Table 1

Age	Lymphoma type	Stage	PS	HIV	CD4	Alternating regimen	RT	Sustained Response (months)	Progression (months)	Death (months)
34	DLBCL	IVB	3	+	4	-	-	PD	1.0	1.3
49	BL	IVB	2	+	91	EPOCH	-	CR (50)	-	-
40	BL	IIA	2	-	-	hCVAD	+	CR (57)	-	-
51	DLBCL	IVB	2	+	47	EPOCH	-	CR (65)	-	-
40	BL	IVB	2	+	214	hCVAD	-	PD	2.0	-
34	PBL	IVB	2	+	16	-	-	PD	1.0	4.5
33	PBL	IIA	1	+	166	EPOCH	-	CR (18)	-	-
44	PBL	IVA	1	+	458	EPOCH	-	CR (19)	-	-
52	PBL	IIB	1	+	57	EPOCH	+	CR (20)	-	-
51	Solid PEL	IVB	2	+	113	-	-	CR (31), 2nd CR (10)	After 1st line: 31.1	-

PS: ECOG performance score; RT: radiotherapy; DLBCL: diffuse large B-cell lymphoma; PEL: primary effusion lymphoma; PBL: plasmablastic lymphoma. EPOCH: etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; hyper cVAD: dexamethasone and fractionated vincristine, doxorubicin cyclophosphamide; CR: complete remission; PR: partial remission; PD: progressive disease.

*Correspondence: jramos2@med.miami.edu
[1]Division of Hematology/Oncology, University of Miami Miller School of Medicine, Miami, FL, USA
Full list of author information is available at the end of the article

clinical responses and even cures in patients with poor prognosis gamma-herpes virus-related lymphomas.

Materials and methods

Ten patients with EBV-positive (9 HIV-positive) non-Hodgkin's lymphoma (NHL) were treated with first-line MTX (3.0-4.5 g/m^2 IV on day 1) and AZT 1.5 g IV infusion q12 hours (days 1-4) every 3 weeks or alternated with other chemotherapy regimens, including EPOCH, or hyper cVAD between 2004-2009 at the discretion of the treating physician (Table 1). One patient (solid PEL) received AZT and MTX initially, and upon relapse 31 months later received DOX 20 mg/m^2 (Day 1) , MTX 5 g/m^2 (Day 2), and AZT 750 mg twice daily with hydroxyurea 1 g daily (Days 2-5) under our new clinical trial.

Results

Clinical characteristics, response, and survival data of patients are summarized in Table 1. All patients were treated with high-dose AZT and MTX. Three patients with plasmablastic lymphoma (PBL) and 1 patient with BL also received alternating EPOCH; 2 BL patients received alternating hCVAD. Seven patients achieved CR. Two patients developed neutropenic fever. Median PFS in this cohort of patients has not been reached. Median OS was 31 months (95% CI: 0.0-84.8).

Conclusions

The combination of high-dose MTX/AZT is a promising and tolerable treatment for gamma-herpes virus-related lymphomas. A Phase II clinical trial with low-dose doxorubicin, MTX, AZT, and hydroxyurea for relapse EBV+ NHL is currently recruiting participants. Interim results and supporting laboratory data for using this gamma-herpes virus lytic approach will be presented at the meeting.

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Author details

[1]Division of Hematology/Oncology, University of Miami Miller School of Medicine, Miami, FL, USA. [2]Department of Microbiology and Immunology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA.

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