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621.LYMPHOMAS: TRANSLATIONAL-MOLECULAR AND GENETIC

Genetic Alterations of Follicular Lymphoma Can Predict Response to Very Low Dose Radiotherapy

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Introduction
Follicular lymphoma (FL) is typically indolent, but relapses and transformation to higher grade disease are common. FL is often radiosensitive and can show complete response (CR) even to very low dose radiotherapy (VLDRT, 4Gy). There are no known genetic markers of FL radiosensitivity. We sought to identify molecular signatures of FL radiosensitivity to aid in patient selection for VLDRT.
Methods
We analyzed our institutional database and identified 110 FL patients with 113 tumors treated with radiotherapy (RT) and pre-existing MSK-IMPACT, a targeted exon sequencing panel. For each patient, we collected key clinicodemographic information including pre- and post-RT treatment history, prior large cell lymphoma, and Ann Arbor stage at RT. For treated tumors, we obtained tumor site, grade, diameter, maximum SUV, *BCL2* translocation (trans) status through fluorescence in situ hybridization, RT dose and fractionation, and the treatment strategy (*i.e.* treating all sites of disease vs a subsite of disease). Tumor site was dichotomized by pelvic tumors vs all others, as this was the most frequently altered site. The presence of mutant (mut) genes compared to wild type (WT) were associated with RT response, measured by PET scan within 6 months of RT, using logistic regression. Log-rank testing and Cox proportional hazards models were used to analyze local progression free survival (LPFS), censored at start of unplanned therapy, with 2-year (2y) survival reported. Multivariate modeling was used to adjust gene associations with outcomes, controlling for the clinicodemographic and tumor characteristics mentioned above.
Results
The patient and tumor characteristics are summarized in table 1. We found *CREBBP* to be the most frequently altered gene (66% of tumors). We identified 5 signatures of altered genes, most of which showed altered *CREBBP* and relatively long LPFS (e.g. one signature showed *CREBBP* mut, *TNFRSF14* mut and *IRF8/STAT6* mut with a 2y LPFS 78%); however, one signature with concurrent *KMT2D* mut and altered *BCL2* including trans and mut had significantly shorter LPFS than all other signatures (2y LPFS 47%, $p < 0.01$) and lower odds of CR relative to the other signatures ($p= 0.03$). *CREBBP* mut was the only alteration associated with increased odds of CR (Odds ratio: 2.39 (95% CI: 1.06-5.37, $p = 0.04$), and this effect remained significant after adjusting for pelvic disease site ($p=0.04$). Mutations of *BCL2*, *IRF8*, and *KMT2D* were associated with LPFS using log-rank testing ($p<0.01$, $p=0.02$, and $p=0.04$, respectively). *BCL2* mut or concurrent *BCL2* mut and *BCL2* trans (mut/trans) had shorter LPFS for the overall cohort ($p<0.01$ for both), while for VLDRT, only *BCL2* mut/trans was associated with shorter LPFS ($p=0.02$). In the VLDRT cohort, we found that *CREBBP* histone acetyltransferase (HAT) mut was associated with improved

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LPFS compared to WT (n=39, 2y LPFS 74% vs 52%, HR:0.41 (95% CI: 0.18-0.93, p=0.03)), but this was not observed for tumors receiving >4Gy (n=44, HR: 1.27 (95% CI: 0.32-5.08), p=0.74)). We observed that either *BCL2* mut, *BCL2* trans, or *BCL2* mut/trans and CREBBP HAT WT had a 2y LPFS of 13% whereas *BCL2* mut, *BCL2* trans or *BCL2* mut/trans and *CREBBP* HAT mut had a 2y LPFS of 83% (p<0.01), and this relationship persisted on multivariate analysis (Figure 1).

Conclusions

Incorporating genetic signatures associated with radiosensitivity, and specifically alterations involving *BCL2* and *CREBBP*, may independently improve patient selection for RT. *CREBBP* HAT domain mutations are potentially targetable and may have important implications for augmenting radiosensitivity to VLDRT.

Disclosures Lebow: *Oncia Technologies, Inc:* Current equity holder in publicly-traded company. **Joffe:** *Beigene:* Honoraria; *Abbvie:* Honoraria. **Dogan:** *Seattle Genetics:* Consultancy; *Physicians' Education Resource:* Consultancy, Honoraria; *EUSA Pharma:* Consultancy; *Loxo:* Consultancy; *Peer View:* Honoraria; *Incyte:* Consultancy; *Takeda:* Other: Research Funding; *Roche:* Other: Research Funding. **Zelenetz:** *BeiGene:* Consultancy, Honoraria, Research Funding; *BMS:* Consultancy, Honoraria; *None other than mutual funds (401K):* Current equity holder in publicly-traded company; *F. Hoffmann-La Roche Ltd:* Consultancy, Honoraria, Research Funding; *SAB:* Membership on an entity's Board of Directors or advisory committees; *AstraZeneca:* Consultancy, Honoraria; *MEI Pharma Inc:* Consultancy, Honoraria, Research Funding; *Lymphoma Research Foundation:* Membership on an entity's Board of Directors or advisory committees; *Janssen Pharmaceuticals:* Consultancy, Honoraria; *Pharmacyclics:* Consultancy, Honoraria; *Abbvie:* Research Funding; *Gilead:* Consultancy, Honoraria. **Salles:** *Janssen:* Consultancy, Research Funding; *Nurix:* Consultancy; *Ipsen:* Consultancy, Research Funding; *Orna:* Consultancy; *Nordic Nanovector:* Consultancy; *BeiGene:* Consultancy; *BMS/Celgene:* Consultancy; *Debiopharm:* Consultancy; *ATB Therapeutics:* Consultancy; *Kite/Gilead:* Consultancy; *Merck:* Consultancy, Honoraria; *Molecular Partners:* Consultancy; *Incyte:* Consultancy; *Novartis:* Consultancy; *Loxo/Lilly:* Consultancy; *Genmab:* Consultancy; *Genentech, Inc./F. Hoffmann-La Roche Ltd:* Consultancy, Research Funding; *Owkin:* Current holder of *stock options* in a privately-held company; *EPIZYME:* Consultancy; *AbbVie:* Consultancy, Honoraria. **Imber:** *GT Medical Technologies:* Honoraria. **Yahalom:** *Convergent R.N.R Ltd.:* Other: Provision of Services (uncompensated).

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Table 1. Tumor and treatment characteristics for full cohort, VLDRT cohort, and >4Gy cohort

Variable	Category	Full cohort (n=113 tumors) n (%) or median (range)	VLDRT cohort (n=67 tumors) n (%) or median (range)	>4Gy Cohort (n=46 tumors) n (%) or median (range)	P-value
Irradiated site	Lymph nodes (non-pelvic)	34 (30%)	23 (34%)	11 (24%)	
	Pelvis	43 (38%)	15 (22%)	28 (61%)	0.002
	Other soft tissue	22 (19%)	17 (25%)	5 (13%)	
	Parotid	5 (4%)	5 (7%)	0 (0%)	
	Orbit	5 (4%)	4 (6%)	1 (2%)	
	Bone	4 (4%)	3 (4%)	1 (2%)	
RT dose (Gy)	4	67 (59%)	67 (100%)	.	
	12-20	4 (4%)	.	4 (9%)	.
	24	19 (17%)	.	19 (41%)	
	>24	23 (20%)	.	23 (50%)	
FL grade*	Grade 1-2	91 (81%)	58 (88%)	33 (72%)	0.057
	Grade 3A	21 (19%)	8 (12%)	13 (28%)	
Diameter	Maximum diameter	3.2 cm (0-11.9 cm)	3.3 cm (0.7-8.0 cm)	3.2 cm (0.0-11.9 cm)	0.222
SUV	Maximum SUV	9.2 (0 – 19.7)	8.8 (0-19.7)	9.5 (0-18.4)	0.364
PET staged pre-RT	PET Staged	106 (94%)	63 (94%)	43 (93%)	0.999
	Staged with other imaging modalities	7 (6%)	4 (6%)	3 (7%)	
Stage at RT	Early stage	79 (70%)	39 (58%)	40 (87%)	0.002
	Advanced stage	34 (30%)	28 (42%)	6 (13%)	
Treatment Strategy	Comprehensive	39 (35%)	15 (22%)	24 (52%)	0.002
	Subset of disease treated	74 (65%)	52 (78%)	22 (48%)	
Prior large cell lymphoma	Yes	8 (7%)	7 (10%)	1 (2%)	0.139
	No	105 (93%)	60 (90%)	45 (98%)	
Prior Chemoimmunotherapy	Yes	47 (42%)	28 (42%)	19 (41%)	0.999
	No	66 (58%)	39 (58%)	27 (59%)	
Prior transplants	Yes	3 (3%)	1 (1%)	2 (4%)	0.164
	No	110 (97%)	66 (99%)	44 (96%)	

*One patient did not have FL grade assessed on their pathology report

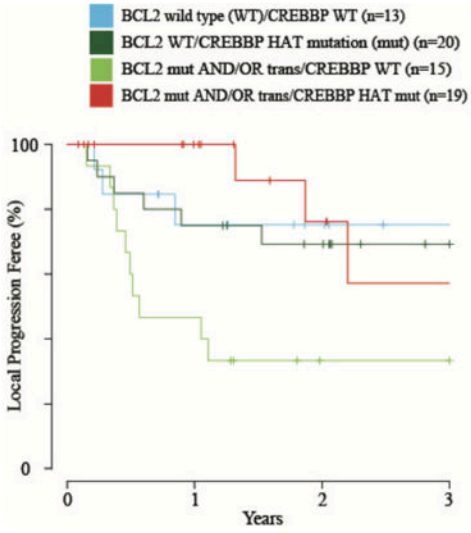

Figure 1. The combined effects of BCL2 mutation, BCL2 translocation, and CREBBP HAT mutation in patients treated with very low dose radiotherapy.

Figure 1

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