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Expression of CD30 as a biomarker to predict response to brentuximab vedotin

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Sir: CD30 is a transmembrane receptor in the tumour necrosis factor receptor superfamily, member 8 (TNFRSF8) that was first identified in the malignant Hodgkin and Reed-Sternberg (HRS) cells of classical Hodgkin lymphoma.[1] Brentuximab vedotin (SGN-35; BV) is an antibody–drug conjugate used currently in the setting of CD30-positive relapsed or refractory lymphomas. This study demonstrates our experience of relative CD30 expression with tumour response to BV.

Biopsies were collected from all patients receiving BV at our institution. Most recent biopsies from tumour at the time of relapse were reviewed independently by two haematopathologists. Antigen retrieval was performed using a Ventana kit. Rabbit monoclonal antibody to CD30 (clone BerH2, 1:300; Epito-mics, Burlingame, CA, USA) was used.

The percentage of CD30-positive cells of total cellularity, the percentage of CD30-positive cells of the tumour population and the stain strength (mild, moderate, marked) were estimated. The association of each variable with either complete response (CR) or complete and partial response (PR) was evaluated using univariate logistic regression analysis. All calculations used SAS statistical analysis software (SAS Institute Inc., Cary, NC, USA). Two-tailed *P*-values <0.05 were considered significant.

Patient and tumour characteristics are listed in Table 1. All patients received BV as single agent at 1.8 mg/kg by intravenous infusion once every 3 weeks for a maximum of 16 cycles or until disease progression or toxicity. Clinical response was assessed at average intervals of 3 weeks, 8 weeks and 1 year after starting therapy.

Reduction in tumour burden was seen in 17 of 25 patients. The overall response rate (ORR) was 72%, with 44% achieving CR. In patients with non-Hodgkin lymphomas (NHL), 78%

Ethics approving committee

Yale Human Research Protection Program Human Investigation Committee #1201009533. First approved 1/17/2012; last re-approved: 1/17/2015. This study fulfilled the criteria for waiver of informed, written consent. It was performed according to the Declaration of Helsinki.

Conflict of interests

The authors have no conflicts of interests or sources of funding to disclose.

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achieved a response and 50% CR. In classical Hodgkin lymphoma (CHL), the ORR was 64% while CR was seen in 36%.

Positive immunostaining for CD30 assessed as a percentage of total cellularity, or of the percentage of tumour cells showed no correlation with clinical outcome in either NHL or CHL. The strength of CD30 stain on tumour cells showed no association with response in NHL patients. However, in CHL there was a trend of increased response with increased stain strength. Statistical analyses were repeated to assess for correlation between all variables mentioned above at the approximate 1-year interval, which showed no significant correlation. Figure 1 demonstrates the staining patterns of a few of these cases.

Results of logistic regression analysis using clinical response as outcome are represented in Table 2. Odds ratios greater than 1 indicate that with each increase in scoring level of 1 unit (in %CD30 staining or stain strength), there is an increased probability of clinical response.

CD30 is expressed on the cell surface of a wide range of lymphomas, but few non-malignant cells, providing a rational therapeutic target. Although limited by a small sample size, we find that the level of CD30 expression detected by immunohistochemistry is not a good predictor of clinical response to BV. The efficacy demonstrated in our institution is comparable to a large Phase II trial showing an ORR of 75% and CR of 34%.[2] A recent study showed a significant correlation between CD30 mRNA levels to CD30 immunohistochemical scores using an identical anti-CD30 antibody clone to the one used here.[3]

Computer-assisted methods of CD30 detection have been evaluated. A study of 49 diffuse large B cell lymphomas (DLBCLs) in a multi-institutional clinical trial reported no correlation between response and expression of CD30, similar to our findings.[4] Interestingly, some tumours negative by visual examination proved to have a quantifiable level of CD30 expression by computer-assisted methods. Unfortunately, computer-assisted methods are not available routinely for clinical use and may not be practical to implement.

Multispectral imaging (MSI) provides another method of possibly increasing sensitivity to low-level CD30 expression. In a Phase II trial of BV in cutaneous T cell lymphoma (CTCL), it was shown that objective clinical response was seen regardless of visual CD30 expression. Some of the positivity visualized later by MSI was found to be co-expressed by elements of the microenvironment, such as macrophages and cytotoxic T cells.[5]

In conclusion, our study demonstrates a lack of correlation between clinical outcome and CD30 expression on tumour cells as assessed by immunohistochemistry. As such, it may not be rational to use this marker for strict enrolment purposes. Larger, multi-institutional efforts are necessary to validate these findings. The potential that BV activity may be independent of the level of CD30 expression is worth additional investigation in order to elucidate its mechanism and identify eligible patients more effectively.

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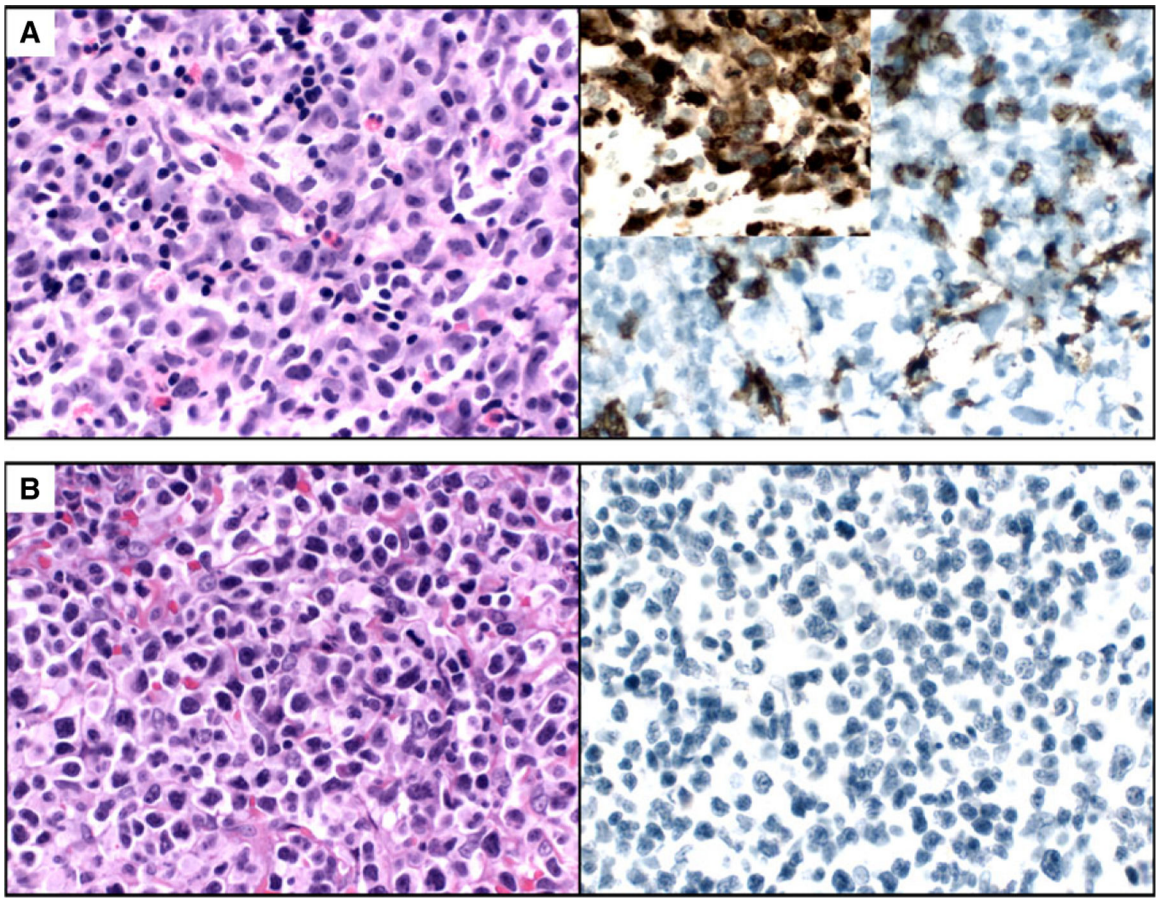

Figure 1.

A, Case 7 showing CD30 staining of ~70% of T cell lymphoma cells (inset shows CD3 stain). The patient achieved partial remission. B, Case 1 showing CD30 staining of ~0% of T cell lymphoma cells. The patient achieved complete remission.

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Table 1.

Clinicopathological characteristics

Case	Diagnosis	Gender	Age (years)	Site of disease	Marrow involvement	Prior therapy	Best response	% CD30 overall	% CD30 of tumour
Non-Hodgkin lymphomas									
1	AITL	F	79	LN	Positive	CHOP/ICE/Denileukin diftitox/Pralatrexate	CR	0	0
2	AITL	M	62	LN	Negative	CHOP	CR	20	35
3	ALCL, ALK+	M	80	Soft tissue	Positive	Denileukin diftitox/XRT	CR	8	95
4	ALCL, ALK−	M	24	LN	Positive	EPOCH/AutoSCT	CR	15	100
5	cALCL	M	63	Tonsil	Negative	CHOP/methotrexate	CR	18	95
6	PTCL, NOS	M	33	Skin	Negative	Gemcitabine/Romidepsin/Pralatrexate/ EPOCH	PR	0	0
7	CTCL	F	55	LN	Negative	Photopheresis/Targretin	PR	50	70
8	PTCL, NOS	M	63	LN	Positive	CHOP/AlloSCT/Pralatrexate	CR	5	10
9	CTCL	M	71	LN	Negative	Total skin irradiation/AlloSCT	CR	0	0
10	CTCL	M	66	Skin	NA	Methotrexate/Targretin/Photopheresis	SD	0	0
11	CTCL	F	62	Skin	NA	CHOP/Denileukin diftitox/Methotexate/ Targretin	PR	45	45
12	CTCL	F	70	Tonsil	NA	Photopheresis/IFN-alpha/Targretin/ Romidepsin/Pralatrexate/EPOCH	SD	85	97
13	DLBCL	F	20	LN	Negative	R-CVP/R-EPOCH	PD	20	40
14	DLBCL	F	86	Bone	Positive	CEOP	SD	0	0
15	DLBCL	M	49	Soft tissue	Positive	EPOCH-R/RICE/DHAP	PR	30	80
Hodgkin lymphomas									
16	CHL	M	18	LN	Positive	ABVD/ICE/AutoSCT/COPP/R-DHAP/ EPOCH	PR	18	100
17	CHL	F	21	LN	Negative	ABVD/DHAP/ICE/Auto-SCT/C-MOPP/ Bendamustine	PR	12	100
18	CHL	M	84	LN	NA	ABVD	CR	5	100
19	CHL	F	23	LN	Negative	ABVD/BEACOPP	CR	65	100
20	CHL	F	65	liver	Negative	ABVD	PD	10	100
21	CHL	M	38	LN	NA	ABVD/ICE/AutoSCT/GND/AlloSCT/C-MOPP	CR	25	100

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Case	Diagnosis	Gender	Age (years)	Site of disease	Marrow involvement	Prior therapy	Best response	% CD30 overall	% CD30 of tumour
22	CHL	F	28	LN	NA	ABVD/ICE/AutoSCT	CR	25	100
23	CHL	M	89	Lung	NA	None	PD	40	100
24	CHL	M	28	Mediastinal	Positive	ABVD/C-MOPP/AlloSCT	PD	78	100
25	CHL	F	54	Mediastinal	NA	ABVD/ICE	SD	3	100
26	CHL	M	54	LN	Negative	ABVD/ICE/AutoSCT	SD	4	100
27	CHL	M	33	LN	NA	ABVD/ICE/AutoSCT	PR	5	100

CR: Complete remission; PR: partial remission; SD: stable disease; PD: progressive disease; LN: lymph node; AITL: angioimmunoblastic T cell lymphoma; ALCL: anaplastic large cell lymphoma; cALCL: cutaneous anaplastic large cell lymphoma; PTCL NOS: peripheral T cell lymphoma, not otherwise specified; CTC:, cutaneous T cell lymphoma; DLBCL: diffuse large B cell lymphoma; CHL: classical Hodgkin lymphoma; R: rituximab; CHOP: cyclophosphamide, hydroxydaunorubicin, oncovine, prednisone; EPOCH: etoposide, prednisone, vincristine, cytoxan, doxorubicin; CEOP: cyclophosphamide, vincristine, epirubicin, prednisone; ICE: ifosfamide, carboplatin, etoposide; DHAP: dexam-ethasone, cytarabine, cisplatin; ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine; COPP: cyclophosphamide, oncovin, procarbazine, prednisone; MOPP: mechlorethamine, vincristine, procarbazine, predisone; BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; GND: gemcitabine, vinorelbine, doxorubicin; CVP: cyclophosphamide, vincrinstine, prednisone; XRT: radiation therapy; SCT: stem cell transplant.

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Table 2.

Logistic regression analysis of CD30 positivity for clinical response to brentuximab vedotin

	CR			CR+PR		
	Odds ratio	**CI**	***P***	**Odds ratio**	**CI**	***P***
All samples (*n* = 27)						
% CD30 of the cellularity	1.04	(0.79, 1.35)	0.774	1.29	(0.65, 2.56)	0.472
Stain strength	0.67	(0.17, 2.67)	0.574	2.49	(0.58, 10.66)	0.220
Non-Hodgkin lymphoma (*n* = 15)						
% CD30 of the cellularity	0.00	(<0.001, 83.11)	0.232	0.00	(<0.001, 9.86)	0.155
% CD30 of all tumour	0.06	(0.002, 1.98)	0.115	0.13	(0.002, 10.39)	0.357
Stain strength	0.19	(0.02, 2.4)	0.199	1.00	(0.10, 10.073)	1.000
Classical Hodgkin lymphoma (*n* = 12)						
% CD30 of the cellularity	1.09	(0.82, 1.45)	0.543	1.67	(0.29, 9.54)	0.563
Stain strength	1.93	(0.14–26.79)	0.625	5.90	(0.46–76.64)	0.174

CR, Complete remission; PR, partial remission; CI, confidence interval.

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