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LETTER TO THE EDITOR

Ibrutinib has some activity in Richter's syndrome

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Richter's syndrome (RS), defined as the transformation of chronic lymphocytic leukemia (CLL) into an aggressive lymphoma, is seen in about 2–10% of all CLL patients.[1] The prognosis of RS is extremely poor with a median survival of about 6 months,[2] although patients with clonally unrelated RS may have a better prognosis.[1] No randomized controlled trials exist to date regarding therapeutic strategies in these patients. Data from phase I/II single-arm studies testing various therapeutic strategies have shown limited survival benefit with significant toxicity.[2–6] Here, we present two cases of RS treated with a novel therapeutic agent, ibrutinib (Table 1).

Patient A was a 60-year-old male diagnosed with Rai stage IV CLL after evaluation of progressive lymphadenopathy. Fluorescence *in situ* hybridization (FISH) showed no deletion of ataxia telangiectasia mutated gene, chromosome 11q (ATM), chromosome 13q14.3, or p53. One month later, he developed rapidly progressive lymphadenopathy that upon biopsy revealed clonally related, activated B-cell type (ABC) diffuse large B-cell lymphoma (DLBCL) with a proliferating index Ki-67 of 50% consistent with RS. He was treated with cycles of rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone (R-CHOP), rituximab/ifosfamide/carboplatin/etoposide (RICE) and rituximab/gemcitabine/oxaliplatin; however, his disease was refractory to these conventional therapeutic regimens. He was not a candidate for allogeneic hematopoietic stem cell transplantation due to a lack of insurance. Thus, the patient was started on ibrutinib. One month later, computed tomography (CT) scan revealed 70% regression of his disease, which improved at 3 months to 90% regression of disease.

Patient B was a 59-year-old male who was diagnosed with Rai stage III CLL after evaluation of anemia with lymphocytosis. He was observed for 8 years until he developed progressive lymphocytosis that required treatment of his CLL with bendamustine/rituximab and fludarabine/cyclophosphamide/rituximab. FISH showed trisomy 12 in 34% of nuclei and deletion of p53 in 40% of nuclei, but deletion of ATM and 13q14.3 were not detected. Subsequently, he developed fever, night sweats and rapidly progressing lymphadenopathy for which biopsy of his right neck lymphadenopathy revealed clonally related, ABC DLBCL with a proliferating index Ki-67 of 90% consistent with RS. He was treated with multiple cycles of R-CHOP and RICE. He had poor prognostic features, given his p53 deletion, high LDH level and bulky disease with lung nodular disease. His lymphoma was refractory to these conventional therapeutic regimens, and he was not a candidate for allogeneic hematopoietic stem cell transplantation due to a lack of insurance. Thus, he was started on ibrutinib. CT scan 2 months later showed 100% progression of his neck adenopathy. Ibrutinib was stopped after 3 months due to refractory disease.

Recent studies have shown that ibrutininb, a potent inhibitor of Bruton's tyrosine kinase receptor, is a viable therapeutic option in cases of relapsed/refactory CLL.[7,8] It remains unclear if this drug is effective against patients with RS as well. In an earlier phase Ib/II study on combination of ibrutinib with ofatumumab, a partial response was seen in two out of three patients with RS.[9] It was not clear that whether these patients had different genetic profiles. In our case, both patients had ABC type DLBCL, which has been shown to have a better response to ibrutinib as compared with germinal center B-cell type DLBCL.[10] However, patient A had an excellent response whereas patient B was refractory to ibrutinib therapy. In contrast to patient A, patient B had high-risk mutations (deletion of p53 and trisomy of chromosome 12) and a high-proliferation index (Ki-67 of 90%) suggesting a poor prognosis. This may suggest that ibrutinib is beneficial in a select group of patients with distinct genetic profiles. Our experience with these patients adds to a growing hypothesis that ibrutinib may be a viable therapeutic option in CLL patients with RS.

Table 1. Summary of previously published phase I/II single-arm studies regarding various chemotherapeutic options for the treatment of Richter's syndrome

Author, year	*Number of patients*	*Therapy type and duration*	*Response rate and toxicity*
Dabaja *et al.*,[2]	*N* = 29, all with RS	Hyper CVXD every 3-4 week intervals for a maximum of six cycles	ORR of 41%, grade IV granulocytopenia occured in all cycles, 14% died during the first cycle of therapy
Tsimberidou *et al.*,[4]	*N* = 22 (16 RS, 3 refractory PLL, 1 refractory NHL)	FACPGM every 4 weeks and continued as tolerated	CRR of 5%, grade III/IV hematologic toxicities in 66–90%, 18% died after the first cycle of therapy[a]
Tsimberidou *et al.*,[3]	*N* = 49 (30 RS, 19 refractory CLL)	Hyper CVXD+R and GM-CSF alternating with methotrexate, cytarabine+R and GM-CSF for upto 6 cycles	ORR of 41%, grade IV neutropenia seen during all cycles, 18% died during the first cycle therapy[a]
Tsimberidou *et al.*,[5]	*N* = 50 (20 RS, 30 refractory CLL)	OFAR every 4 weeks for a maximum of six cycles	ORR of 50% in RS, grade III/IV hematologic toxicities seen in 21–100%
Tsimberidou *et al.*,[6]	*N* = 102, (35 RS, 67 relapsed/refractory CLL)	OFAR2 every 4 weeks for a total of 6 weeks	ORR of 42.9% in RS, grade III/IV hematologic toxicities seen in 49–79%

Abbreviations: CLL, chronic lymphocytic leukemia; CRR, complete remission rate; FACPGM, fludarabine, cytarabine, cyclophosphamide, cisplatin, granulocyte macrophage colony stimulating factor; hyper CVXD, fractionated cyclophosphamide, vincristine, liposomal daunorobicin and dexamethasone; NHL, non-Hodgkins lymphoma; OFAR, oxaliplatin, fludarabine, cytarabine, rituximab and pegfilgastrim; OFAR2, similar to OFAR1 with some dosing modifications; ORR, overall response rate; PLL, pro-lymphocytic leukemia; RS, Richter's syndrome. [a]Response rate of RS patients not separately available.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

MGM compiled the patients treated; all authors wrote the manuscript and contributed to revisions.

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