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Possible novel agents in marginal zone lymphoma

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Venetoclax

A B S T R A C T

Efficacy, safety and mechanisms of action of novel agents in marginal zone lymphoma patients, both with a nodal and extranodal presentation, are reviewed. Data on lenalidomide, bortezomib and ^{90}yttrium-ibrutumomab tiuxetan are obtained from trials specifically designed for patients affected by marginal zone lymphoma and with various disease presentations. The role of targeted agents, such as obinutuzumab, ibrutinib and idelalisib, and of some very new drugs (venetoclax, copanlisib, ublituximab and TGR-1202) is also discussed, taking into account the most relevant experiences in patients with indolent non-Hodgkin's lymphomas. A glance to some possible drug combinations will also be provided, along with an update of the most relevant ongoing trials.

Introduction

Given the heterogeneity and the overall low prevalence of marginal zone lymphoma (MZL), which represents no more than 17% of all non-Hodgkin's lymphomas [1], with mucosa-associated lymphoid tissue (MALT) lymphoma being the most represented type [2], the majority of studies involving new drugs and targeted agents are not specifically addressed to this disease and include just a few patients with this histological subtype.

Current treatment strategies for MZL include radiation and single-agent immunotherapy for early-stage nodal disease and localized extranodal MALT lymphoma [3]. *Helicobacter pylori* (HP)-eradicating antibiotic therapy [4,5] is considered the preferred initial treatment of localized HP-positive gastric MALT lymphoma, and benefits from antibiotic treatment with doxycycline against *Chlamydophila psittaci* have also been reported [6,7]. However, in case of disseminated nodal or extranodal disease, the treatment of choice is yet to be defined [3]: systemic approaches have been applied, also in case of relapsed disease, and chemoimmunotherapy regimens usually applied for follicular lymphoma have been proposed and recently updated [8,9]. The addition of rituximab to chlorambucil has demonstrated effectiveness in patients with MALT lymphoma not responding or not eligible to local therapy [10].

Nevertheless, systemic treatment should be considered carefully, as they generally fail in assuring prolonged remissions, they are not always feasible and may display severe acute and late toxicities. Targeted approaches and newer molecules, used either as single agents or in combination with immunotherapy or chemotherapy, may represent a step forward to the optimization of treatment and will hopefully contribute in establishing new therapeutic standards (Tables 1 and 2).

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Table 1
Summary of the results of targeted agents in patients with marginal zone lymphoma. MZL, marginal zone lymphoma; MALT, mucosa associated lymphoid tissue lymphoma; OAL, ocular adnexal lymphoma; ORR, overall response rate; ^{90}Y-IT, ^{90}Y-ibritumomab tiuxetan; N.R., not reached.

Author	Drug	Setting	Pts	ORR%	CR%	Median PFS ([a])	Toxicity
Kiesewetter [19]	Lenalidomide	MALT de novo + relapsed	18	61	33	–	Neutropenia, pruritus
Fowler [23]	Rituximab + lenalidomide	MZL de novo	30	89	67	53.8	Neutropenia, thrombocytopenia
Troch [31]	Bortezomib	MALT de novo	16	80	43	22.0	Neuropathy, diarrhea
Di Bella [34]	Bortezomib	MZL, MALT relapsed	6	17	17	— ([b])	Thrombocytopenia, neuropathy, diarrhea
Conconi [33]	Bortezomib	MALT relapsed	32	48	31	25.0	Neuropathy
Zinzani [36]	Fludarabine, mitoxantrone + ^{90}Y-IT	MZL, MALT de novo	10	90	90	— ([b])	Neutropenia, thrombocytopenia
Esmaeli [41]	^{90}Y-IT	OAL de novo	9	89	78	–	Thrombocytopenia, anemia
Hoffmann [37]	^{90}Y-IT	MALT relapsed	6	83	67	–	Neutropenia, thrombocytopenia
Vanazzi [38]	^{90}Y-IT	MALT relapsed	30	90	77	N.R. ([c])	Neutropenia, thrombocytopenia
Lossos [40]	^{90}Y-IT	MALT de novo	16	88	56	47.6	Neutropenia, thrombocytopenia
Samaniego [39]	^{90}Y-IT	MZL de novo	11	100	— ([b])	81.8	Neutropenia, thrombocytopenia

[a] Median PFS is given in months.
[b] Data not reported for the specific MZL subtype in a population that also includes follicular lymphoma patients and/or other indolent lymphoma patients.
[c] This indicates time-to-treatment failure.

Table 2
Clinically meaningful experiences with new drugs in patients with MZL. GA101, obinutuzumab; ORR, overall response rate; CR, complete response; PR, partial response; PFS, progression-free survival.

Author	Drug	Setting	MZL Pts	Meaningful findings	Toxicity
Sehn [49]	GA101 *vs* rituximab	Relapsed	6 5	Higher ORR and CR rate with obinutuzumab but not superior PFS	Infusion-related reactions
Sehn [50]	GA101 + benda *vs* bendamustine	Relapsed	27 19	PFS superiority of the obinutuzumab-containing regimen	Infusion-related reactions
Advani [54]	Ibrutinib	Relapsed	4	Active in relapsed and refractory patients across different histologies	Diarrhea, nausea, fatigue, neutropenia
Flinn [58,59]	Idelalisib	Relapsed	6	PR in 33% of cases	Neutropenia, thrombocytopenia, transaminases elevation
Gopal [59,60]	Idelalisib	Relapsed	15	Responses in 47% of cases, mainly PR. Median duration of response of 18.4 months	Neutropenia, transaminases elevation, diarrhea, colitis, pneumonia, pneumonitis

Lenalidomide

Lenalidomide is a thalidomide derivative that works as an immunomodulatory drug at cellular and molecular levels, with also the property of blocking angiogenesis through the inhibition of vascular-endothelial growth factor [11]. More specifically, this drug is able to target the tumor microenvironment, as it enhances the activity of mononuclear blood cells, including T-lymphocytes, and repairs T-cell immunologic synapse dysfunctions [12]; it increases the antibody-dependent cellular toxicity (ADCC) mediated by monocytes and natural killer cells [13]; it modulates the incretion of several cytokines, including tumor necrosis factor-α, interferon-γ and interleukin-12 [11]. It has been demonstrated – at least in multiple myeloma – that lenalidomide binds to its protein target cereblon, which in turns downregulates the expression of Ikaros and Aiolos through their ubiquitination and degradation, and ultimately modulates oncogenically activated pathways of cancer cells, thus inhibiting their growth and inducing apoptosis [14,15].

Lenalidomide has shown efficacy as single agent in patients with high and low-grade non-Hodgkin's lymphoma, either during induction or in the setting of relapsed or refractory disease [16–18]. These studies, however, mainly deal with follicular, diffuse large B-cell lymphoma and mantle-cell lymphoma, therefore the experience in MZL is indeed very limited.

The most relevant study that reports the activity of single agent lenalidomide in patients affected by MALT lymphoma is from Kiesewetter et al. [19]. The treatment consisted of a standard 25 mg oral dose of lenalidomide given daily for 21 consecutive days on cycles repeated every 28 days. The study included patients with non-gastric MALT lymphoma and HP-negative gastric MALT lymphoma, either untreated or with relapsed disease; those with a HP-positive gastric MALT lymphoma who had no response to an eradicative antibiotic treatment after at least 12 months of follow-up were also eligible. Response was assessed after 3 cycles by radiological criteria and by histology on biopsies obtained from gastroscopy (when applicable), and patients with at least stable disease could receive 3 more courses of therapy. Eighteen patients were included in the trial: 7 had ocular-adnexal MALT lymphoma, 5 gastric MALT lymphoma, 3 showed pulmonary disease while the remaining had colic, subcutaneous and parotid gland involvement. Sixteen patients had at least one assessment of response: 11 patients showed an objective response (61%), with a complete response (CR) rate of 33%. Responses were seen in both treatment-naïve and pre-treated patients, and conversions to better responses were documented with continuous therapy in at least 39% of patients. Hematologic side-effects were rare, and just 3 patients experienced grade 3 neutropenia. Among extra-hematologic events, pruritus was the most relevant effect, and an additional exanthema on the trunk was noted in 4 patients.

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