Splenic Marginal Zone Lymphoma

9

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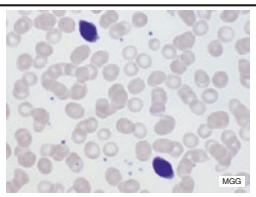
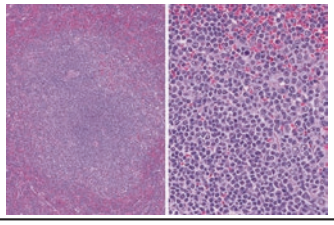
Splenic marginal zone lymphoma (SMZL)

Clinical outline
Primarily the spleen, peripheral blood and bone marrow. Lymph nodes and extranodal sites usually spared. Cytopenia and autoimmune manifestations frequent. Association with HCV infection observed in Southern Europe.

Cytology	In peripheral blood "villous" lymphocytes (small cell with short, polar cytoplasmic projections). In the tissues, range in morphology from centrocyte-like to monocytoid, with variable degree of lymphoplasmacytic differentiation. Few or no blasts.	Splenic marginal zone lymphoma, cytology 
Histology	In bone marrow biopsies, characteristic sinusoidal pattern of infiltration. Splenic histology, effaced white pulp with a biphasic picture (pale ring around residual follicles) and extension into to the red pulp. Frequent infiltration large vessel walls. In lymph nodes, SMZL resembles nodal MZL.	Splenic marginal zone lymphoma, hystology 

	CD20	CD5[1]	CD23[1]	CD10	BCL6	cyclin D1	CD103	FMC7	IgM	light chains
notes	[1]usually partially and/or weak.									
other marker	SMZL lacks a specific phenotype and the antibody panel should be primarily aimed at the exclusion of other lymphoma subtypes.									

= majority of cases positive = variable fraction of cases positive = negative

Main differential diagnosis	HCL (should be CD103 and BRAF V600E positive), CLL (should be CD23 and CD5 positive), MCL (should be cyclin D1 positive). Subtypes of marginal zone lymphomas (extranodal, nodal, splenic, cutaneous) distinguished mainly by clinical presentation (pattern of involved organs).

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Key molecular features Activation of NOTCH and nuclear factor kappa B pathways IGH genes rearranged, somatic hypermutation and IGHV3 and IGHV4 usage bias. Frequent translocations: Non reported. Frequent copy number alterations: Loss of 7q. Frequent mutations: *NOTCH2, KLF2, TNFAIP3, MLL2/KMT2D, MYD88, CARD11*		
Precursor lesions Some cases appear be preceded by monoclonal B-cell lymphocytosisof the non-CLL type (CD5-negative).		
Progression 10-15% progress to high grade lymphoma, typically of the diffuse large B-cell subtype.		
Clinically relevant pathologic features	**Relevance**	**Evidence**
IGHV mutation status	Prognostic: unmutated (unfavorable)	**C**
***M*utations**	Prognostic: *NOTCH2*, *TP53* (unfavorable)	**C**
Hepatitis C	predictive: may respont to anti-viral therapy	
Proliferation/blasts	High proliferation and/or blast content (unfavourable)	**B**
Legend: A = verified in multiple studies, randomized trials and/or integrated in guidelines; B = variable between studies/ needs definitive validation; C = preliminary/discrepant results.		

9.1 Epidemiology

SMZL is a rare B-cell neoplasm, accounting for less than 2% of all lymphomas and about 20% of the marginal zone lymphoma (MZL) subset [1, 2], yet it embodies the most common primary malignancy of the spleen [3]. Gender prevalence varies in different series [4–6], but these differences are lost in large retrospective registries [7]. The median age at diagnosis is 68 years, and nearly all patients are aged greater than 50 years [7, 8]. The overall age-adjusted incidence is 0.13 per 100,000 persons per year, with increasing trends among patients who are white, male, or age ≥70 years. However, the incidence is likely to be underestimated because splenectomy is not routinely performed in all cases of splenic lymphoma, and establishing a precise diagnosis without the examination of splenic tissue may be challenging [9]. Epidemiological data have postulated a possible association between hepatitis C virus (HCV) infection and lymphoproliferative disorders, particularly MZL [10, 11]. Subsequently, the presence of a higher risk of developing lymphoma, particularly MZL or DLBCL, has been confirmed both in areas of high (Overall Relative Risk:2.4; 95% CI: 2.0–3.0) and low HCV infection prevalence (OR:1.6; 95% CI: 1.3–1.9) [12–14]. Also, several groups reported regression or even remission of the lymphoma after successful treatment of HCV chronic infection [15–17]. These findings

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strengthen the hypothesis that HCV might play a role in the lymphomagenesis by driving a chronic antigen stimulation triggered by the virus glycoprotein E2, which in turn stimulates CD81 in B-cells [13]. Other factors reported linked to an increased risk are autoimmune diseases, asthma and permanent use of hair dyes [18].

9.2 Clinical Manifestation

Clinical presentation often consists of isolated splenomegaly with or without cytopenia(s) and or mild lymphocytosis [5, 6, 8, 19, 20]. About one-third of patients are genuinely asymptomatic, and the diagnosis is made by chance after the incidental detection of splenomegaly amidst clinical assessment for unrelated causes [9]. Splenomegaly is usually massive (median longitudinal diameter 20 cm), but in a subset of patients the spleen is relatively small [21]. A small subset of patients presents with an isolated, slight to moderate, lymphocytosis showing the morphology and immunophenotype consistent with the diagnosis of SMZL [22]. This clinical picture overlaps with that of monoclonal B-cell lymphocytosis with marginal zone phenotype (MBL-MZ) [23]. Whether this presentation embodies an indolent SMZL variant or a pre-lymphomatous condition is still an open issue [22–24]. Symptoms, if present, are mostly related to massive splenomegaly, such as abdominal discomfort, early satiety or left flank pain. Slight to moderate anaemia and thrombocytopenia are detected in 50%, 20% and 24% of cases, respectively, mostly due to hypersplenism or autoimmunity, rarely to bone marrow infiltration [25, 26]. Exceptionally, the degree of thrombocytopenia is severe enough to account for haemorrhagic symptoms; neutropenia is definitively rare, usually mild and clinically inconsequential. A leukemic component (defined as the presence of absolute lymphocytosis or >5% neoplastic lymphocytes in peripheral blood) is present in 52–75% of cases [6, 20, 26]. A moderate increase of LDH and beta2 microglobulin concentrations are found in about 30% and 60% of patients, respectively. A small (less than 2 g/dL) monoclonal component (MC), mainly μ (IgM) isotype, is detected in approximately one-third of patients. These patients also frequently display haemolytic anaemia, immune thrombocytopenia or coagulation disorders [4]. In the Mediterranean basin, up to 19% of SMZL patients are carriers of a chronic HCV infection and may show a distinctive presentation trait comprising higher incidence of CM mainly μ (IgM), type II cryoglobulinemia and nodal disease [26]. Saadun reported the association of HCV infection, cryoglobulinemia along with the presence of villous lymphocytes in peripheral blood and proposed it could represent a distinct entity [27]. About 20% of patients show autoimmune manifestations [4, 28]. Autoimmune haemolytic anaemia (AHA), autoimmune thrombocytopenia (AITP) and cold agglutinin disease are the most frequently reported autoimmune disorders and are generally present on diagnosis [6, 20]. Moreover, some patients may show a positive direct antiglobulin test (DAT) without signs of overt AHA. Among other autoimmune manifestations associated with SMZL, the most clinically relevant are acquired C1q deficiency and angioedema [29], acquired coagulation disorders [4], and acquired antiphospholipid antibodies and thrombophilic syndrome [30]. By clinical examination, little can be inferred other than signs related to splenomegaly, because clinically significant peripheral lymphadenopathies are exceptionally detected, and moderate hepatomegaly is reported in only one-third of patients [4, 6, 22].

9.3 Peripheral Blood Cytology

A leukemic component, in the form of slight to moderate lymphocytosis, is quite common. At variance with other lymphoid tumours, leukemic neoplastic cells display a marked morphological heterogeneity shown by the simultaneous presence of small lymphocytes without specific features, lymphoplasmacytic cells, lymphocytes with nuclear clefts, medium-sized lymphomonocytic cells with relative abundant pale cytoplasm and villous lymphocytes [22, 31–33]. In some cases, the prevalent morphology is that of villous lymphocytes, small lymphocytes with round nucleus with thickened chromatin and basophilic cyto-

plasm characterised by the presence of short villi unevenly distributed or concentrated at one of the two poles of the cell [33]. Villi are lost after a few hours of storage of blood; then they can hardly be seen if a peripheral blood smear is not set up timely.

9.4 Bone Marrow

Bone marrow (BM) infiltration is a constant finding in SMZL [2]. Particularly in the early phases of the disease, BM infiltration may be very subtle and difficult to recognise on routine morphologic sections. The BM infiltration pattern may be almost exclusively intrasinusoidal [34], but concurrently with the progression of the disease or after splenectomy a nodular and or interstitial involvement of the intertrabecular space become apparent [35]. Rare and scattered reactive germinal centres surrounded by a rim tumour cells can be found. Neoplastic cells comprise rather monomorphic small- to medium-sized lymphocytes showing round to oval nucleus with regular contour and a small rim of cytoplasm. However, plasmacytoid features with a morphological differentiation gradient from lymphocyte to a plasmacytic cell can be observed in about 20% of cases [2]. While none of the infiltration patterns and morphological aspects described are specific to SMZL, their combination is rather characteristic [36].

9.5 Spleen

The cut surface of the spleen displays a micronodular white miliary-like pattern as a result of the neoplastic infiltration centred on pre-existing follicles. Microscopic examination shows pre-existing lymphoid follicles infiltrated or substituted by small B-lymphocytes with round or slightly irregular nuclei effacing the follicle mantle zone. In the outer peripheral part of the follicle, the marginal zone, neoplastic cells are of medium size and have a clear pale cytoplasm giving rise to a distinctive biphasic picture [2, 37]. Scattered transformed blasts outline the follicle marginal zone and can infiltrate the red pulp intermingled with small B-lymphocytes and marginal zone-like cells [38]. A variable degree of lymphoplasmacytic differentiation can be found with micronodular or patchy infiltration pattern in the marginal zone, characteristically in germinal centres, and the red pulp [39].

9.6 Immunophenotype

SMZL clonal B-cells do not express a specific immunophenotype. All neoplastic cells consistently express CD20, CD79a, BCL2 and variably DBA44 and are negative for CD10, BCL6, cyclin D1/BCL1, CD43 and annexin A1. SMZL cells carry surface immunoglobulin IgM and IgD with moderate to strong intensity [2, 40]. About 15% of cases are CD5 positive, and 20% of cases may express CD23. CD5 expression correlates with higher lymphocytosis and diffuse infiltration pattern of the bone marrow [41]. The Matutes flow cytometry score [42] is low in SMZL, ranging from 0 to 2.

9.7 Genetic and Biomolecular Landscape

SMZL displays a high genomic complexity [43]; genetic aberrations are documented in over 70% of patients and are complex in 53% of cases (defined as ≥3 aberrations or ≥2 clones). Although no specific genetic alteration has been described so far, deletions of chromosome 7q are quite characteristic [44, 45], occurring with significantly higher frequency (30–40%) in SMZL than in other lymphoid neoplasms. Also, there are a plethora of recurring abnormalities shared with other MZL subtypes. These include gains of 3q, 9q, 12q and 18q, and losses of 6q, 8p, 14q and 17p- [43, 46]. At variance with most other B-cell lymphomas, in SMZL, specific recurrent chromosomal translocations are not described. The immunoglobulin heavy chain variable region (IGVH) genes mutational analysis show that only 15% of cases carry truly unmutated IGVH. In mutated cases, the load of somatic hypermutation ranges from minimal (97–99.9% germline iden-

tity) to pronounced [47–50]. Furthermore, the analysis of immunoglobulin genes shows a highly restricted gene repertoire and biased use of the IGVH allele IGHV1–2*04 in 25–40% of cases [47, 51]. Most of these rearrangements (95%) have a low mutational load (97–99.9% germline identity) of conservative nature and restricted distribution. A parallel picture has emerged from the investigation of the clonotypic immunoglobulin light chains revealing restrictions in both kappa (IGKV) and lambda (IGLV) variable gene repertoires [52]. Most of these rearrangements display a minimal mutational load (97–99.9% germline identity) and a long CDR3 sequence with common motifs. Moreover, a stereotyped configuration of the B-cell receptor (BCR) has been detected in 10% of cases [53]. Overall, these findings strongly point to a possible selection of T-cell-independent MZ B-cells by superantigens and suggest that an antigenic drive might play a role in SMZL development [54, 55]. Whole-exome sequencing in SMZL reveals an expression signature consistently characterised by upregulation of genes involved in MZ cell differentiation and circulation between the functional compartments of the lymphoid tissues [56–60]. Recurring mutations in SMZL can be classified into three main groups: NOTCH signalling, nuclear factor kB (NF-kB) pathway, chromatin remodelling and the cytoskeleton [54, 61]. Inactivating mutations of the Krüppel-like factor 2 (KLF2) zinc finger gene occur in 20–40% of SMZL cases [56, 57], resulting in the most frequent somatic change detected in SMZL. Mutated KLF2 delocalises from the nucleus into the cytoplasm and is not able to inhibit the NF-κB activation by upstream signalling, including the BCR and TLR pathways. Interestingly, KLF2 lesions frequently co-occur with IGHV1–2*04 usage, NOTCH2 mutations, and 7q deletions. NOTCH2 and NOTCH1 genes are mutated in 10–25% and 5% of SMZLs, respectively; mutations and truncations cluster in the C-terminal PEST domain thus leading to enhanced stability of the active NOTCH intracellular domains [58, 59]. Overall, considering mutations in negative regulators of NOTCH signalling (such as SPEN, DTX1, and MAML2), upregulation of the NOTCH pathway by genetic events occurs in up to 40% of SMZLs. Since NOTCH2 mutations appear to be very rare in other B-cell lymphomas except for DLBCL (5%), in an appropriate clinical contest they turn out to be specific for SMZL. Mutations activating NF-κB signalling are reported in 34% of cases and are mutually exclusive with that of NOTCH pathway. Mutations occur both in genes of canonical and non-canonical NF-kB pathways (TRAF3, MAP3K14, TNFAIP3, IKBKB, BIRC3) and of coding members of upstream pathways of the BCR (CARD11), and TLR (MYD88) [62]. Mutations were also found in chromatin remodeler genes such as MLL2 (6/40 cases), ARID1A (2/40), and SIN3A (3/40), and more frequently in CREBBP and TP53 (15% of cases) [59]. Methylation changes described in SMZL are associated with silencing of diverse tumour suppressor genes and over-expression of genes involved in BCR/PI3K/AKT/ NF-κB signalling [61, 63]. Finally, an SMZL miRNA signature has been described, targeting some of the key genes and pathways involved in NF-kB activation and B-cell survival. The pattern of miRNA expression is different in HCV positive cases, also showing downregulation of miR-26b, a miRNA with tumour suppressor activity [64].

9.8 Diagnosis

A vast and heterogeneous array of lymphoid neoplasms may show limited or prevalent homing and growth in the spleen. The definition of splenic lymphomas encompasses cases with splenic involvement and in which the disease may also extend to the BM, peripheral blood and the liver, in the absence of prominent lymph node involvement [65]. Some lymphoid neoplasms typically occur confined to the spleen, whereas for others, this presentation is a possible and rare clinical variant (Table 9.1). While presenting clinical, laboratory, pathologic and immunophenotypic features of such lymphomas display significant overlaps, clinical course, biological characteristics and outcomes differ significantly ranging from indolent to very aggressive [9]. Thus, to establish an accurate diagnosis of SMZL is of

Table 9.1 Primary splenic lymphomas (PSL)

(a) Lymphomas commonly presenting as PSL
• Splenic marginal zone lymphoma
• lymphoma/leukemia unclassifiableSplenic diffuse red pulp B-cell lymphomaHairy-cell leukemia variant
• Hairy cell leukemia
• Lymphoplasmacytic lymphoma
• B-cell prolymphocytic leukemia
• T-cell large granular lymphocytic leukemia
• Hepatosplenic T-cell lymphoma
(b) Primary nodal lymphomas occasionally presenting as PSL
• Mantle cell lymphoma
• Follicular lymphoma
• Diffuse large B-cell lymphoma not otherwise specified
• Micronodular T-cell/histiocyte rich large B-cell lymphoma

Splenic lymphomas encompass cases with splenic involvement and in which the disease may also extend to the bone marrow, peripheral blood, and the liver, in the absence of prominent lymph node involvement

Table 9.2 Criteria for coding clinical response in SMZL

Response to splenectomy	
	All the following: • At least 50% improvement on the blood counts • Non-progressive lymphocytosis • No change or improvement in the degree of BM infiltration
Response to systemic treatment	
PR	*50% or greater improvement in the disease manifestations*: • Resolution or decrease in spleen size • Improvement on cytopenias • Resolution or decrease in lymphadenopathy if present • BM should show a decrease in the level of lymphoid infiltration and improvement of the hemopoietic reserve
CR	*All the following*: • Resolution of organomegaly • Normalization of the blood counts § • No evidence of circulating clonal B cells • No evidence or minor BM infiltration detected by immunohistochemistry
NR	Less than 10% improvement on the disease manifestations or deterioration of the above, respectively.

PR partial remission, *CR* complete remission, *NR* no response

[a]Haemoglobin >120 g/L; platelets > 100×10^9 L^{-1}; neutrophils >1.5×10^9 L and no evidence of circulating clonal B cells)

paramount importance for the different appropriate treatment strategies, prognosis and outcomes of these other lymphomas. Spleen histology still is the reference for the diagnosis of SMZL. However, splenectomy is a major surgical procedure with morbidity mostly due to perioperative complications, late infections and even mortality [66, 67]. On the clinical ground, in a substantial proportion of splenic lymphomas, splenectomy could be not advised and or not have a therapeutic role [68]. The SMZL study group (SMZLSG) provided an expert guideline aimed to establish the diagnosis of SMZL when information on the spleen histology is not available [22]. Indeed, consistent integration of BM histological and immunohistochemical findings with the results of the various clinical, laboratory investigations, including peripheral blood morphology, immunophenotype, genetics and molecular biology, usually allows for diagnosis with a reasonably high level of confidence. The differential diagnosis in some instances is particularly challenging, such as that between SMZL and lymphoplasmacytic lymphoma in patients that have a serum IgM monoclonal paraprotein and or show lymphoplasmacytic differentiation. Yet after such a thorough and integrated examination, in some cases only a generic diagnosis of B-cell chronic lymphoproliferative disorder can be reached [9, 36, 69]. In such instances, if the differential diagnostic problem should affect treatment choices and outcome expectations, it is required to resort to splenectomy to reach a definite diagnosis.

9.9 Staging and Prognostic Scores

SMZL has a peculiar way of presentation, diffusion and evolution. The criteria for staging and evaluation of the response to therapy proposed by the SMZLSG still constitute a reference (Table 9.2). SMZL is not conceived as a fluorodeoxyglucose avid disease [70] and should routinely be staged through computed tomography. The use of fdg-PET scans could be clinically useful when-

ever an evolution towards aggressive histology is suspected. Nevertheless, the role of fdg-PET [71] and new imaging techniques, such as whole-body MRI [72] in staging and response assessment, has not been specifically investigated yet. SMZL is a neoplasm with a rather favourable prognosis given that about two-thirds of patients are alive five years after the diagnosis [26, 73] and about 20% do not need any therapy for several years. However, around 20% of patients experience a more aggressive course and shorter survival. Understandably, the different and particular features of presentation and diffusion make the prognostic scores built for the other lymphoproliferative neoplasms unsuited for SMZL. The first specifically conceived clinical scoring system was developed by the Intergruppo Italiano linfomi (IIL, now Federazione Italiana Linfomi: FIL) on 309 SMZL patients with a 5-year cause-specific survival (CSS) rate of 76%. The prognostic score was built by selecting the three variables with the highest hazard ratios for a shorter CSS, (haemoglobin <12 g/dL, elevated LDH and albumin <35 g/dL). By using these variables, three prognostic groups were identified: low-risk (no adverse factor), intermediate-risk (one adverse factor) and high-risk (two or more adverse factors) with statistically different 5-year CSS ($P = 0.001$) of 88%, 73% and 50%, respectively [26]. Interestingly, the high-risk group intercepted 54% of all lymphoma deaths. Subsequently, the SMZLSG proposed a risk stratification system based on the assessment of four variables developed on a large series of 593 patients [25]. The score was named HPLL, after the determinant factors H (haemoglobin), P (platelet count), L (LDH) and L (extra-hilar lymphadenopathy) found in correlation with a shorter lymphoma specific survival (LSS). According to the number of variables, three groups were identified: A (no adverse factor), B (1 or 2 adverse factors) and C (3 or 4 adverse factors) with survival at five years of 95%, 87% and 68%, respectively. In the HPLL score both haemoglobin and platelets are accounted as a continuous variable to obtain the best fit, and the application of the score requires a calculation by a formula; thus a simplified version of the prognostic score was developed to make more comfortable its use in daily clinical practice [74]. To this end, the same four risk factors were used, and clinically acceptable cut-off points of 9.5 g/dL for haemoglobin level and 80×10^9 L^{-1} for platelet count were established. Patients with 0, 1, 2, 3 or 4 factors were separated in a final set of three groups: A: 198 patients (0); B: 311 patients (1 or 2); C: 41 patients (3 or 4) with 5-year LSS significantly different among the three risk groups. Recently, Kalpadakis et al. have validated this simplified HPLL score in an independent series of SMZL patients, confirming its ability in identifying subgroups of SMZL patients with a significantly different outcome [75]. However, clinical scores are surrogate markers which imperfectly intercept disease outcome differences. Thus, a great effort has been focused on studies aimed to explore the prognostic value of biomolecular markers. Parameters that have been associated with adverse outcomes are p53 mutation, 7q deletion, NOTCH2 mutation and the absence of somatic mutation in IgVH genes and aberrant promoter methylation [43, 47, 58, 76–78]. However, other studies have reported conflicting results [59, 79].

9.10 Therapy

Diverse therapeutic options, including splenectomy, chemotherapy, rituximab monotherapy and chemoimmunotherapy, produce clinical responses and effective control of SMZL-related symptoms. However, no prospective randomised study specifically designed for SMZL has been conducted so far, and there is no clue that any of the proposed therapies can appreciably modify the natural history of the disease [73, 74, 80]. Furthermore, the comparison of retrospective studies is made particularly difficult by the lack of prospectively validated prognostic scores and uniform criteria for initiation of therapy. According to the recently updated ESMO guidelines [81], and expert statements [9, 22, 54], only symptomatic patients should receive treatment. Currently, effective palliation should be pursued by rituximab monotherapy or with splenectomy if it is deemed necessary also for diagnostic purposes [81].

9.11 Watchful Waiting

About 20–30% of newly diagnosed SMZL patients are asymptomatic [4–6], can remain stable for several years and there is no evidence that they would benefit from early therapeutic intervention. In the large retrospective series of SMZLSG [25], 161 patients (27%) had not received any treatment and only three of them (1.8%) ultimately died of lymphoma. These data support the reliability and safety of adopting a watchful and waiting strategy in asymptomatic patients and suggest avoiding splenectomy for mere diagnostic purposes. Patients in vigilant waiting policy may be followed every 3–6 months with a physical examination, blood counts and biochemistry [9, 22]. SMZL patients showing an active HCV infection constitute the exception to the "no move" strategy described for asymptomatic patients, and antiviral treatment should be considered as a first-line treatment [81, 82].

9.12 HCV Antiviral Treatment

In a seminal observation, Hermine et al. showed that interferon-based antiviral treatment (AVT) can induce haematological response along with virological clearance in patients with HCV-associated splenic lymphoma with villous lymphocytes [15]. Subsequently, the association of interferon with ribavirine has been confirmed effective in several series of HCV-associated lymphomas, and particularly MZL [83]. Further, a recent a meta-analysis on 20 studies of IFN-based antiviral therapy (AVT) in patients with HCV-associated B-NHL showed that the response rate was 73% in all patients and up to 83% in those who attained a sustained virological response (SVR) [84]. A better lymphoma response was shown in MZL compared to no-MZL (81% vs.71%). A direct anti-lymphoma activity of interferon cannot be ruled out, particularly in MZL. Nevertheless, recent data on the efficacy of new IFN-free regimens with direct-acting antivirals (DAA) in a retrospective series of 46 HCV-associated lymphoproliferative disorders suggest their anti-lymphoma activity [85]. The median duration of DAA therapy was 12 weeks (range, 6–24 weeks). An SVR after finishing DAAs was obtained in 45 patients (98%): the overall lymphoproliferative disease response rate (LDR) was 67%, including 12 patients (26%) who achieved a complete response. The LDR rate was 73% among patients with MZL, whereas no response was observed in CLL/SLL patients. Seven patients cleared cryoglobulins out of 15 who were initially positive. After a median follow-up of 8 months, 1-year progression-free and overall survival rates were 75% (95% confidence interval [CI], 51–88) and 98% [95% CI, 86–100], respectively. DAA therapy induces a high LDR rate in HCV-associated indolent lymphomas. These data strongly support a causative role of HCV in lymphomagenesis and prospective trials with DAAs in this setting are underway.

9.13 Who Needs Anti-neoplastic Treatment?

Treatment should be initiated in patients with symptomatic splenomegaly, cytopenia(s), systemic symptoms or progressive nodal disease [22, 81]. These criteria are clinically sound but have not been prospectively validated yet. Noteworthy, three of these criteria (lymphatic adenopathy, anaemia and thrombocytopenia) are independently associated with LSS and were incorporated in the HPLL risk stratification for SMZL. Consensus guidelines suggest that autoimmune cytopenias should be specifically treated and antiviral treatment should be considered in patients with concurrent active HCV chronic infection with HCV-related hepatitis who do not need immediate conventional treatment against the lymphoma [81, 85].

9.14 Splenectomy

Splenectomy provides the tissue for diagnosis and has been considered the first-choice treatment for SMZL in the pre-rituximab era [32, 80] Indeed, after surgery, a quick relief from pressure-and volume-related symptoms (abdominal discom-

Table 9.3 Series of SMZL reporting splenectomy as first-line therapy

Year-author	# of pts	ORR	PFS % (at *n* years)	OS % (at *n* years)	Surgery related deaths
1991-Mulligan et al.	20	96	Median 4 years	NR	1
1996-Troussard et al.	28	75	NR	71 (5)	1
2002-Chacon et al.	60	93	Median 40 months	65 (5)	NR
2002-Thieblemont et al.	48	100	Median 4 years	NR	NR
2003-Parry-Jones et al.	33	NR	NR	95 (10)	NR
2004-Iannitto et al.	21	91	Median 4 years	NR	NR
2006-Tsimberidou et al.	10	60	Median 4 years	83 (3)	0
2012-Olszewski et al.	652	NR	80 (3)	67.8 (5)	NR
2013-Kalpadakis et al.	27	86	58 (5)	77 (5)	1
2014-Lenglet et al.	100	97	61 (5)	84 (5)	0
2015-Xing et al.	52	NR	39 (10)	61 (10)	0
2015-Pata et al.	41	90	35 (5)	75 (5)	0

ORR overall response rate, *PFS* progression-free survival, *OS* overall survival

fort, early satiety) and complete or partial recovery of cytopenia(s) are expected in all and up to 90% of patients, respectively [4, 6, 86, 87]. Though clinical responses to splenectomy are not complete since extra-splenic disease persists, they are durable; published series report a 5-year PFS of approximately 35–61% and OS ranging from 61% to 75% (Table 9.3). However, these data should be taken cautiously because in many series of splenectomised patients post-splenectomy chemotherapy has been delivered in a significant proportion of cases. Furthermore, splenectomy does not modify the natural history of the disease, and particularly the risk of histologic transformation into DLBCL, which ranges between 11% and 14% in the largest series [43, 86]. Finally, splenectomy is a major surgical procedure and is associated with morbidity and even a low-risk of mortality. Perioperative complications in surgical series on SMZL occur in 25–35% of patients and are mostly due to pulmonary dysfunction and major bleeding [88, 89]. Although perioperative mortality is <1%, significant long-term mortality of about 5% due to infectious complications is reported [86, 87]. Therefore, a possible indication for the therapeutic splenectomy should be limited to patients complaining of symptoms related to the presence of splenomegaly (abdominal discomfort and or hypersplenism), minimal bone marrow disease, absent nodal involvement and without lung comorbidities. Immunisation against encapsulated bacteria is mandatory in all patients at least 2 weeks before elective surgery and sepsis prevention measures must be maintained throughout life [90].

9.15 Chemotherapy

Single-agent chemotherapy has been used in the past mainly in patients relapsed to splenectomy and or with advanced disease, often extended to lymph nodes and analysed in small retrospective series; a detailed and comprehensive analysis on this topic is reported elsewhere [31]. Alkylating agents proved to be not effective, while purine analogues produced a significant number of complete clinical responses though at the expense of haematological and infectious toxicity. These data are now outdated by rituximab therapy, and chemotherapy alone is no longer recommended as first-line treatment.

9.16 Rituximab Monotherapy

Bennet's 2005 report on the efficacy of the anti CD20 monoclonal antibody rituximab in a series of 11 SMZL patients has paved a new way in the treatment of SMZL [91]. Several other retrospective series have subsequently shown that rituximab monotherapy yields up to 90% of clinical responses, half these responses being complete even at molecular level, with minimal toxicity (Table 9.4). Furthermore, in many cases after relapse, rituximab re-treatment is still effective. On these premises, according to the ESMO guidelines, rituximab monotherapy is a reasonable first-line treatment as effective and less traumatic than splenectomy [81]. The Italian Society of Hematology guidelines specifies that rituximab monotherapy is the therapy of choice for patients without disseminated disease who need treatment and unfit for splenectomy [85]. In a large series of consecutively treated patients, Kalpadakis et al. [92] first reported that the 5-year overall and progression-free survival (PFS) rates for rituximab-treated and splenectomised patients were comparable: 92% and77% (p = 0.09) and 73% and 58% (p = 0.06), respectively, and that 2-year maintenance therapy with rituximab resulted in a longer duration of response (at 5 years, PFS was 84% for patients receiving maintenance and 36% for patients without maintenance, p = 0001). This study has been recently updated and extended to 108 patients [93]. The overall response rate after the end of induction treatment was 92% (CR 44%; Cru 21%; PR 27%). Rituximab maintenance therapy, one shot every two months for two years, improved the quality of response in 16/77 patients: 14/22 (64%) patients in PR achieved either CR (n5) or Cru (n11). The outcomes were remarkable: the 5- and 10-year FFP rates were 71% and 64%; the 5- and 10-year OS rates were 93% and 85%, and the 5- and 10-year LSS rates were 99% and 90%, respectively. PFS was significantly better in patients who received maintenance (7-year PFS 75% for patients who received maintenance vs. 39% for those who did not, $p < 0.0004$) but no difference in OS was noticed between patients who received maintenance and those who did not.

9.17 Chemoimmunotherapy

Rituximab in combination with chemotherapy (R-chemo) is the standard of care for the treatment of indolent lymphomas, but due to toxicity concerns, the indication for SMZL is currently limited to fit patients with suspected histological transformation and or with constitutional symptoms [81, 85] or disseminated disease. Seven clinical studies, five retrospective [94–98] and two prospective [99, 100], dedicated to investigating the role of R-chemo in SMZL have been published so far (Table 9.5). Overall, the accumulated experience on a total of 302 patients suggests that the R-chemo yields higher CR rates and comparable duration of response and PFS [96, 97, 99, 100] rates than rituximab monotherapy [93, 94]. In 2015, the FIL group published the first multicentre prospective study dedicated to SMZL. Fifty-one patients with SMZL were treated with a modified R-CHOP: rituximab, cyclophosphamide, vincristine, non-pegylated liposomal doxorubicin and prednisone (R-COMP). The ORR and

Table 9.4 Rituximab monotherapy

Year-author	# pts	Patients Status	ORR	CRR	PFS % (at *n* years)	OS % (at *n* years)
2005-Bennet et al.	11	RR	91	NR	60 (5)	60 (5)
2006-Tsimberidou et al.	25	First-line	88	31	86 (3)	86 (3)
2007-Kalpadakis et al.	16	First-line	100	69	92 (2.4)	92 (2.4)
2012-Else et al	10	RR and First-line	100	90	89 (3)	89 (3)
2013-Kalpadakis et al.	58	First-line	95	45	73 (5)	73 (59)
2018-Kalpadakis et al	104	First-line	92	47	64 (10)	88 (10)

RR relapsed or resistant, *ORR* overall response rate, *CRR* complete response rate, *PFS* progression-free survival, *OS* overall survival

Table 9.5 Rituximab plus chemotherapy

Year-author	Patients status	Schema	# pts	Response		Survival	
				ORR, %	CRR, %	FFS/PFS/DOR (at *n* years)	OS (at *n* years)
2006-Tsimberidou	First-line	R-chemo	6	83	34	FFS 100% at 3 years	100% at 5 years
2010-Cervetti	RR and First-line	R-2CdA	47	87	62	PFS 80% at 5 years	83% at 3 years
2012-Else	RR and First-line	R-chemo	33	100	70	DSF 71% at 3 years	NR
2015-Iannitto[a]	First-line	R-COMP	51	84	65	PFS 54% at 6 years	72% at 6 years
2017-Cervetti	First-line	R-CTX	30	87	70	20 months (median)	(10)
2017-Castelli	First-line	R-Benda	70	86	70	DOR 18 months (median)	NR
2018-Iannitto[a]	First-line	R-Benda	65	91	73	PFS 90 at 3 years	96% at 3 years

[a]Prospective study; *ORR* overall response rate, *CRR* complete remission rate, *OS* overall survival, *FFS* failure-free survival, *mth* months, *PFS* progression-free survival, *DOR* duration of response, *R* rituximab, *benda* bendamustine, *Chemo* chemotherapy, *CTX* cytoxan, *COMP* cytoxan, oncovin, myocet, prednisone, *2CdA* 2-chlodesoxyadenosine

CR rates were 84% and 65%, respectively; 6-year PFS was 54% and OS was 72%. Overall, toxicity was R-CHOP alike, moderate and manageable but two toxic deaths were recorded (grade >3 neutropenia, 26%; grade >3 infections, 8%; two deaths as a result of infection). A large amount of data indicates the association bendamustine-rituximab (BR) as an effective regimen with an acceptable toxicity profile on almost the entire spectrum of indolent lymphomas [101]. Recently, two studies have explored the role of this association in SMZL [97, 101]. In a retrospective analysis of 70 consecutive SMZL patients treated with BR, 60 patients (86%) achieved a complete response (CR), and seven (10%) a partial response (PR). Three patients (4.3%) experienced disease progression (PD). The median duration of remission was 18 months. Side effects were generally mild [97]. These promising results were prospectively confirmed by the IELSG36/BRISMA study [101]. Sixty-five patients received BR at standard doses q28 and were restaged after three cycles: those patients in CR received a further BR cycle as consolidation while those in PR completed the entire six-course cycles. The OR and CR rates were 91% and 73%, respectively. DOR, PFS and OS at 3 years were 93% (95CI 81–98), 90% (95CI 77–96) and 96% (95CI 84–98), respectively. Toxicity was mostly haematological. Neutropenia G ≥ 3 was recorded in 43% of patients, infections and febrile neutropenia in 5.4% and 3.6%. Most of the non-haematological toxicities were G ≤ 2. Furthermore, more than half of the patients examined achieved molecular remission. A molecular marker was found in 43/54 (80%) cases and MRD negativisation rates were 47% at interim restaging (BM: 13/32; PB: 21/36), 54% at completion of treatment (BM: 10/23; PB: 18/22) and 61% after 1 year (BM:14/22; PB: 19/29) [102].

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