been hypothesized that interference with niche-induced quiescence, either by altered niche signaling or detachment from the niche, may result in increased cycling of cells that have the inherent machinery of self-renewal, thus poising these cells ready for the acquisition of somatic mutations and malignant transformation. Recently experimental evidence introduced the concept of niche-induced oncogenesis in the hematopoietic system, showing that specific genetic abnormalities in osteoprogenitor cells can induce myelodysplasia and acute myeloid leukemia in mice.[19] Whether leukemic transformation in this system was associated with impaired trafficking or aberrant localization of HSC in their niche remains to be determined. It is noteworthy, however, that aberrant localization of hematopoietic stem/progenitor cells in human disease is not unprecedented, as atypical localization of immature progenitors is a common finding in myelodysplastic syndromes.[20] Indeed, recent findings in mouse models warrant reconsideration of a possible involvement of the dynamic interaction between HSC and their niche in the pathogenesis of certain hematopoietic diseases, including bone marrow failure syndromes and myelodysplastic syndromes. Studies such as the one published by Staudt *et al.* in this issue of the Journal, identifying determinants of this interaction, will greatly facilitate such investigations.

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Biological diversity and risk-adapted treatment of chronic lymphocytic leukemia

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(Related Original Article on pages 1519 and 1526)

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in the western world. Unlike other forms of leukemia, the proliferative component of CLL is relatively small, but recent evidence has pointed to the existence of a proliferative pool, which can be surprisingly sizeable.[1] There are several additional features of CLL that set it apart from other cancers. The most prominent pathogenic mechanisms include: (i) genomic aberrations targeting critical genes (e.g. miRNA, *TP53*, *ATM*); (ii) antigen drive and stereotyped B-cell receptors (BCR); and (iii) microenvironmental stimulation.[2,3] While the precise sequence of events is currently unclear, our growing understanding of CLL biology is enabling translation into clinical practice.

The papers by Marincevic *et al.*[4] and Giné *et al.*[5] in this issue of *Haematologica* touch on two important issues in

Table 1. Summary of current prognostic factors and potential treatment options in patients with chronic lymphocytic leukemia and an indication for first-line treatment.

	Risk factor	Incidence (first-line treatment situation)	Treatment approach
Ultra high risk (~10-15%)	17p deletion	~ 5-8%	Clinical trial with investigational agent acting independently of p53, allogeneic stem cell transplantation
	TP53 mutation	~4-5%	
	Fludarabine-refractory CLL	~ 5-10%	
High risk (~70%)	unmutated *IGHV*	~ 60%	
	V3-21 usage	<1%	
	high β-2M (TK)		
	11q deletion	~20%	FCR, maintenance trials, investigational agents + FCR
Low risk (~20%)	mutated *IGHV* (and none of the above)	~22%	FCR, De-escalation in clinical trials

β-2M, β2-microglobulin; TK, thymidine kinase; FCR, fludarabine + cyclophosphamide + rituximab.

CLL biology as well as clinical care and thus significantly expand our conception of aspects of this disease.

Biological diversity of chronic lymphocytic leukemia

Different levels of somatic hypermutation of the *IGHV* (and *IGKV*) divide patients with CLL into two clinical subgroups with different prognoses (*IGHV* mutated and unmutated CLL).[6,7] In addition to variable mutations in the IG variable regions, CLL display a remarkably biased *IGHV* gene repertoire (e.g. *IGHV1-69*, *IGHV4-34*, *IGHV3-23* and *IGHV3-21*)[8] and several groups have reported multiple CLL subsets with similar BCR often arising from the use of common H and L chain V region gene segments that share CDR3 structural features. These 'stereotyped' BCR occur in up to 30% of patients.[2] The striking degree of structural restriction of the entire BCR in CLL suggests that common antigens are recognized by CLL cells and support the contribution of an antigen-driven process.

Certain stereotyped BCR have also been indicated to have distinct clinical features. For instance, *IGHV4-34/IGKV2-30* patients with stereotyped BCR appear to have an indolent disease course compared to that of CLL patients with non-stereotyped *IGHV4-34*. Patients with *IGHV3-21* with either stereotyped or non-stereotyped BCR have been suggested to have an inferior overall survival, independently of *IGHV* mutational status.[9]

In the work presented in this issue of the Journal, Marincevic *et al.*[4] assessed genomic aberrations by 250k single nucleotide polymorphism arrays to discover imbalances of genetic aberrations between the different subsets (V3-21; V4-34). While the numbers of cases is too low to draw firm conclusions, a pattern is emerging, which continues on the theme of earlier work showing a high incidence of high-risk genetics (11q-) in cases with unmutated *IGHV* and low-risk aberrations (13q- single) in cases with mutated *IGHV*.[10] A similar scenario is described in the analysis by Marincevic *et al.*, in which low-risk aberrations were present in *IGHV4-34/IGKV2-30* patients with stereotyped BCR (subset #4), while higher risk aberrations (11q deletion and potentially increased numbers of aberrations) were more common in *IGHV3-21* patients. While the findings are interesting and raise a number of challenging questions concerning the sequence of events in CLL pathogenesis, the different groups with stereotype subsets (e.g. *IGHV3-21*) were quite small. In a recent analysis from the UK LRF CLL4 trial, 40/532 patients had *IGHV3-21* usage (0.75%). This suggests that particular emphasis should be paid to the identification of surrogate markers for particular *IGHV* usage groups and stereotyped BCR, which may be a prerequisite for broader clinical application of the findings.

The biological diversity of CLL is also exemplified in a clinically very relevant study presented in this issue of the journal by Giné *et al.*,[5] who analyzed tissue biopsies from 100 patients with CLL. The biopsies were taken because of the suspicion of disease transformation. High grade transformation of CLL remains one of the most difficult to treat "complications" of CLL and we are only slowly identifying predisposing factors and underlying mechanisms. One pattern emerging is that cases in which the malignant clones are unrelated based on *IGHV* usage appear to behave more like *de novo* diffuse large B-cell lymphoma (DLBCL), while clonally related cases may have a dismal prognosis with survival in the range of months.

In the analysis by Giné *et al.*, the biopsies showed histological transformation to DLBCL in 22% of cases. In the remaining 78% patients, the presence of expanded proliferation centers (judged by their size and Ki-67) predicted poor outcome. Based on this assessment, 23% of patients were considered to have "accelerated" CLL defined based on expanded proliferation centers, a mitosis count of greater than 2.4 or Ki67 greater than 40% per proliferation center. The median survival from biopsy of patients with "non-accelerated" CLL, "accelerated" CLL and transformed DLBCL were 76, 34, and 4.3 months, respectively. While the pathogenic mechanism underlying the evolution to accelerated CLL remains to be identified, the study by Giné *et al.*[5] is of practical relevance because it clearly points to the clinical importance of the newly described category of "accelerated" CLL.

Risk-adapted treatment in chronic lymphocytic leukemia

Over recent years our better understanding of genetic and biological groups in CLL has improved risk stratification of patients with this disease. The ultimate goal of risk-adapted approaches in cancer is genotype- or risk factor-adapted therapy in all patients. This depends on the identification of the prognostic and predictive factors of strongest clinical impact. It is important to point out that this is not necessarily identical to what is generally considered a "strong" prognostic marker based on statistical

assessments. The most powerful prognostic factors in CLL include age, Binet or Rai stage, serum markers (β2-microglobulin and thymidine kinase), and genetic factors (genomic aberrations, *IGHV* mutation status, and *TP53* mutations). Nonetheless, even the most reliable prognostic markers may not immediately translate into practice changes. While the *IGHV* mutation status reliably identifies two groups of patients of roughly similar size, this information is not currently changing treatment approaches outside clinical trials. However, future treatment strategies may target deregulated signaling pathways specifically in *IGHV* unmutated (or mutated) CLL.

In contrast, the first genotype-specific treatment for CLL patients has been developed for cases with 17p deletion who have a very poor prognosis (median survival of less than 2 years from first treatment indication) with alkylator and nucleoside-based chemo(immuno)therapy (chlorambucil, fludarabine, fludarabine + cyclophosphamide, or fludarabine + cyclophosphamide + rituximab).[11] Since a number of agents have been shown to act independently of functional p53 in CLL, current treatment approaches in clinical trials use these agents upfront with early allogeneic stem cell transplantation as consolidation after remission has been achieved in eligible patients. In addition to CLL with 17p deletion, the group of patients with *TP53* mutations (even in the absence of 17p deletion) is a subgroup gaining increasing attention.[12] *TP53* mutations are found in 8-12% of patients with an indication for first-line treatment. The incidence increases during the course of disease and was 37% in a cohort of fludarabine-refractory cases.[13] In a recent study within the German CLL4 study (which compared fludarabine and fludarabine + cyclophosphamide treatment), the incidence of *TP53* mutations in the absence of 17p deletion was similar to that of 17p deletions and the clinical course of patients with these forms of CLL was very similar.[14] These data – as well as information from a number of retrospective cohort studies – suggest that *TP53* mutation should be added to the diagnostic work-up of patients with CLL in need of treatment.

Table 1 summarizes different risk categories for CLL patients and potential treatment approaches. Patients with 17p deletion, *TP53* mutation or fludarabine-refractory CLL have a very short overall survival once treatment is indicated.[14,15] These patients are prime candidates for investigational approaches even if previously untreated. In addition, fit patients are candidates for allogeneic stem cell transplantation.[16]

Based on a number of studies including prospective trial data,[17-19] patients with unmutated *IGHV*, 11q deletion, *V3-21* usage and high levels of serum markers (e.g. β-2 microglobulin) form a high-risk group with a median survival in the range of 53 months following an indication for first-line treatment. These patients are now generally treated with the combination of fludarabine + cyclophosphamide + rituximab (if fit and younger), but future trials may consider maintenance strategies in such patients.[20]

The group of patients with none of the above aberrations and mutated *IGHV* status have a very favorable outcome and could even be considered for de-escalation studies.

In spite of this clinically relevant risk hierarchy, the decision to treat is currently not based on the risk profile but on symptomatic disease.[21] This is important and further supported by the observation that in some subgroups of patients, such as those with 17p deletion (and mutated *IGHV*), the disease may have an indolent course.[22]

While risk-adapted treatment approaches are generally used interchangeably with different treatments for certain prognostic risk groups, future risk-adapted treatment strategies will undoubtedly also have to integrate the patient's performance status, co-morbidities and age, which is of particular importance considering that the median age at diagnosis is over 70 years old.

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Pathogenesis and treatment of acquired idiopathic thrombotic thrombocytopenic purpura

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(Related Original Article on page 1555)

Thrombotic thrombocytopenic purpura (TTP) is a rare thrombotic disease characterized by episodes of thrombocytopenia and microangiopathic hemolytic anemia due to disseminated microvascular thrombosis. TTP was first described in 1924 by Moschowitz as a disease presenting with a pentad of signs and symptoms (anemia, thrombocytopenia, fever, hemiparesis and hematuria).[1] Post-mortem examination showed widespread thrombi, mainly composed of platelets, in the terminal circulation of several organs. The description of von Willebrand factor (VWF) multimers of unusually large size in the plasma of patients with TTP represented a turning point for the understanding of the disease pathophysiology.[2,3] The presence in plasma of the highly platelet-adhesive unusually large multimers of VWF provided a plausible explanation for the platelet- and VWF-rich thrombi observed in the small vessels of patients with TTP. Studies in the late 1990s then independently demonstrated the severe deficiency of a specific VWF cleaving-protease in the plasma of patients with recurrent TTP.[4] This protease was identified as the thirteenth member of the ADAMTS (a disintegrin and metalloprotease with thrombospondins 1 repeats) family of metalloproteases, ADAMTS13.[5-7] Severe ADAMTS13 deficiency can be due to mutations in the *ADAMTS13* gene (congenital TTP)[8] or to anti-ADAMTS13 autoantibodies (autoimmune TTP).[9-11] The antibody-mediated severe deficiency of ADAMTS13 can be detected in most patients with idiopathic TTP (i.e. TTP occurring without associated clinical conditions/events), whereas its prevalence is much lower in the secondary forms of TTP (i.e. TTP associated with pregnancy, infections, autoimmune diseases and the use of drugs such as ticlopidine and clopidogrel).[12,13] It should also be mentioned that there are idiopathic cases of TTP with only slightly deficient or even normal ADAMTS13 levels at presentation, but these cases are not object of the present article in which idiopathic and autoantibody-mediated TTP are used as synonyms.

Epidemiology and clinical course of idiopathic thrombotic thrombocytopenic purpura

The incidence of idiopathic TTP is estimated to be 4.5/1 million person/years, being higher in blacks. The male to female ratio is 1:2, similarly to the ratio for other autoimmune diseases.[14] The acute prognosis of idiopathic, antibody-mediated TTP tends to be less severe, but the risk of recurrent disease is higher than that of secondary forms.[15,16] The overall mortality of TTP was higher than 90%, but has decreased to 8-30% after the introduction of plasma exchange, which is the treatment of choice of acute TTP episodes.[17-20] The lower mortality of patients with idiopathic TTP (21% *versus* 39% in the frame of the Oklahoma TTP registry[16]) is probably due to the higher response to plasma exchange of patients with autoantibodies and to the mortality related to associated conditions in secondary cases.[21] Up to 40% of patients with TTP develop recurrent episodes of the disease, with the risk of recurrences being higher in patients with severe ADAMTS13 deficiency and anti-ADAMTS13 autoantibodies during acute episodes.[15,16,22-24] The cumulative risk of recurrence at 7.5 years after the first episode in patients with ADAMTS13 activity below 10% at presentation was estimated to be 41%, 10 times that of patients with activity above 10% (4% risk at 7.5 years).[16] Persistence of ADAMTS13 deficiency and of autoantibodies during disease remission is also associated with increased risk of recurrence.[25,26]