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Review

Clonal relationship of relapsing lymphoid neoplasms

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Summary. Lymphomas encompass a broad spectrum of neoplasias. Traditionally it has been assumed that recurrent neoplasia, especially lymphoma, represents a relapse of the original clone. However, this concept has been challenged.

Here we present an overview of novel perceptions regarding the clonal relationship of relapsing lymphoid neoplasms, i.e. precursor cell acute lymphoblastic lymphoma/leukemia (ALL), so called non-Hodgkin lymphomas (NHL) and classical Hodgkin lymphoma (cHL) and discuss the potential implications of these findings. In ALL, approximately 10% of "relapses" were found to be clonally unrelated to the original disease. In NHL, small series and case reports showed the occurrence of meta- or synchronous lymphoid malignancies, which were of different clonal origin. In cHL, there is evidence that both early and late "relapses" may constitute to a certain proportion a novel neoplasm of different clonal origin too. These findings warrant further investigations in order to verify and strengthen the existing data and might have important clinical implications because novel clonally unrelated lymphomas imitating relapses could possibly be treatable with less aggressive regimens compared to true recurrences.

Key words: Clonality, Recurrence, Non-Hodgkin Lymphoma, Classical Hodgkin Lymphoma, Acute Lymphoblastic Leukemia/Lymphoma

Introduction

Lymphomas are a heterogeneous group of neoplasms, most of which usually respond to treatment. However, a substantial number of patients will experience a recurrence. In general, lymphoma relapses are considered to represent a recurrence of the original neoplasm. Since acquired treatment resistance is anticipated in such instances, more aggressive therapy protocols are usually applied.

However, the concept that all recurrences of a lymphoid neoplasm represent a true relapse of the original disease has been challenged (Mullighan et al., 2008; Obermann et al., 2011) for at least two reasons: First, treatment and outcome have improved significantly over the past decades. Therefore, more patients are likely to survive their first disease event and have the "chance" of experiencing a second neoplasia or a relapse. Second - and probably more important - the invention and broad availability of molecular techniques help to get more profound insights into the genetic background and diversity of neoplasms.

In epithelial tumors it has long been recognized that recurrences do not always represent a true "relapse" of the initial tumor. The number of true recurrences in breast cancer has been estimated at 87%, which means that approximately 13% of second tumors represent novel primaries (Gentilini et al., 2009). These numbers can be calculated from the incidence of contralateral breast cancer and from the numbers of multifocal or multicentric primary tumors as well (Holzel et al., 2011). Accordingly - and in contrast to lymphoid neoplasms - bilateral syn- or metachronous breast tumors are not automatically regarded to be manifestations of the same malignant clone, although they arise in the same type of tissue. Such multiple syn- or metachronous carcinomas are often explained by the so called field effect, i.e. carcinogenic influences, which affect the same type of tissue and make them susceptible to cancer development. Molecular evidence for this field effect has been found in diverse organs such as breast, prostate, and liver (Dakubo et al., 2007; Heaphy et al., 2009; Utsunomiya et al., 2010). In addition, it has been shown in different types of carcinomas by molecular techniques such as microsatellite analysis and comparative genomic hybridization that "relapses" are in fact novel primaries (Chen et al., 2000; Santoro et al., 2003; Regitnig et al.,

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2004).

Here we present an overview of novel perceptions in the field of clonal relationships of relapsing lymphoid neoplasms, i.e. precursor cell acute lymphoblastic lymphoma/leukemia (ALL), so called non-Hodgkin lymphomas (NHL) and classical Hodgkin lymphoma (cHL) and discuss potential clinical implications.

Precursor cell acute lymphoblastic leukemias/ lymphomas

ALL are aggressive lymphoid neoplasms, mostly occurring in children. ALL can be cured by polychemotherapy in the majority of cases (Pui et al., 2008). However, if ALL relapse, the cure rates drop to approximately 30% (Einsiedel et al., 2005; Rivera et al., 2005). Genetic differences have been noted between ALL at first presentation and recurrences (Raimondi et al., 1993; Klumper et al., 1995; Maloney et al., 1999; Irving et al., 2005; Mullighan et al., 2008). These differences are usually attributable to therapy-driven clonal selection and ongoing mutations (Raimondi et al., 1993; Taylor et al., 1994; Marshall et al., 1995; Davi et al., 1996; Maloney et al., 1999; Rosenquist et al., 1999; Ford et al., 2001; Germano et al., 2003; Takeuchi et al., 2003; Zuna et al., 2004; Irving et al., 2005; Panzer-Grumayer et al., 2005; Choi et al., 2007). However, genome wide copy number abnormalities (CNA) profiling of original and relapsed ALL has occasionally shown profound genomic differences between the two manifestations, which might not be explainable by clonal selection and/or clonal progression (Li et al., 2003; Zuna et al., 2004; Mullighan et al., 2008). Mullighan and coworkers (Mullighan et al., 2008) assessed 61 cases of relapsing childhood ALL for CNA after enrichment of tumor cells by flow sorting. Interestingly, in 11% of relapsed samples, none of the CNA present in the initial neoplasm were found in the recurrent ALL. A combination of genome wide CNA, lesion specific PCR assays and loss of heterozygocity (LOH) analyses detected a small number of relapsing ALL cases (6%) that showed no relationship with the initial ALL, suggesting that second "*de novo*" ALL clinically imitate "relapses". Thus, the currently dominating thought that all recurrent ALL represent an evolution of the initial manifestation or at least originate from a common "leukemia stem cell" (Notta et al., 2011) is challenged. Whether this should be taken into specific treatment considerations remains to be addressed by properly designed prospective trials, as no studies have so far - to the best of our knowledge - tackled this question.

Non-Hodgkin lymphomas

The so called NHL are a heterogeneous group of neoplasms of either B-, T- or NK-cell origin. B-cell lymphomas are by far the most common and usually respond to therapy. However, a significant number of patients will either not achieve complete remission after initial treatment or experience a relapse. Traditionally, a relapse - even after several years of freedom from disease - is regarded to be a recurrence of the initial neoplasm (Cappelaere, 1998). Especially, tumors occurring within three years after the initial event and with the same morphology are considered to be clonally related recurrences (Coiffier et al., 1999; Shioyama et al., 2000). However, nowadays it is acknowledged that a NHL recurrence even within a shorter period of time with or without different histology might represent a clonally unrelated secondary neoplasm (Libra et al., 2004). Therefore, in the case of recurrent NHL, histological confirmation is recommended (Libra et al., 2004). Histology and immunohistochemistry may help to distinguish between a true relapse and a secondary neoplasm, but they cannot tell these apart with absolute certainty in each case since morphologically and immunophenotypically identical tumors may still be of distinct clonal origin (e.g. Libra et al., 2002). Furthermore, B-cell NHL recurrences might present in the form of another clonally related lymphoma entity as well. Most notably, the transformation of a "low grade" into a clonally related "high grade" lymphoma at relapse as well as vice versa, recurrence of a "high grade" lymphoma as a clonally related "low grade" component, and progression of small lymphocytic B-cell lymphomas (SLL) to clonally related cHL and simultaneous presence of two histologically different lymphomas, which might be clonally related (clonally related discordant lymphomas) are well known phenomena (Zelenetz et al., 1991; Matolcsy, 1999; Matolcsy et al., 1999; Kremer et al., 2003; Fong et al., 2005). Therefore, similarity or change of morphology cannot be taken as definite proof of or against clonal relationship of relapsing lymphoma. Importantly, morphological analysis of composite NHL seems to be of prognostic significance since bone marrow involvement by concordant (morphologically similar) but not discordant lymphoma (morphologically dissimilar) confers a very poor clinical outcome for diffuse large B-cell lymphoma (DLBCL) (Chung et al., 2007; Sehn et al., 2011).

A number of case reports and small series have addressed the question of the clonal relationship between successive lymphomas in the same patient [summarized in (Libra et al., 2004)]. To our knowledge, no comprehensive studies on the clonal relationship of recurring NHL have been performed on large series of patients. The method of choice for proving clonal relationship in lymphomas is the assessment of B-cell receptor (BCR)- and/or T-cell receptor (TCR) gene rearrangements by fragment lengths analysis or sequencing. BCR/TCR rearrangements are early events in the development of B- and T-cells, respectively (Dadi et al., 2009) and therefore all cells arising from a transformed mature (rearranged) B- or T-cell will have the same BCR/TCR fragment length or BCR/TCR-gene sequence. Thus, the analysis of clonal BCR/TCR rearrangements is not only diagnostically helpful but it can prove clonal kinship between relapsing lymphomas

(McCarthy et al., 1990, 1991). There are several reports applying the above mentioned technology, which brought evidence for possible distinct clonal origin of "recurrent" NHL; both "low-grade" lymphomas such as SLL (Matolcsy et al., 1994; Nakamura et al., 2000) or marginal zone B-cell lymphoma (Heintel et al., 2003) recurring as "high-grade" lymphomas, as well as "high-grade" lymphomas recurring as the same entity have been observed [e.g. Burkitt lymphoma (Lister et al., 1996; Sarkodee-Adoo et al., 2001) and DLBCL (Nishiuchi et al., 1996)]. Other examples are DLBCL followed by follicular lymphoma (Nishiuchi et al., 1996), follicular lymphoma followed by Burkitt lymphoma (Campana et al., 1997) or mantle cell lymphoma (MCL) (Libra et al., 2002), and MCL recurring as a clonally unrelated MCL (Libra et al., 2002). The time span between the first lymphoma and the second unrelated lymphoma ranged from 3 months to 15 years; identical sites and different locations were affected by the successive neoplasms [summarized in (Libra et al., 2004)].

The reason for the appearance of two clonally unrelated lymphomas in the same individual is poorly understood. It might be argued that this individual has some underlying genetic defect that confers susceptibility to develop a lymphoid neoplasm. Here, it might be worth specifically studying recurrent lymphomas in patients who have a genetic predisposition of developing malignancies, such as chromosomal breakage- and inborn immune deficiency syndromes (Filipovich et al., 1992; The International Nijmegen Breakage Syndrome Study Group, 2000; Wang et al., 2007; Goldin et al., 2009). In addition, environmental factors can contribute to lymphomagenesis, and - if not eliminated - give rise to more than one neoplasm (Zahm et al., 1992; Hardell, et al., 1994; Trofe et al., 2002; Merhi et al., 2007; Seidler et al., 2007; Ekstrom Smedby et al., 2008; Castillo et al., 2010); examples are chronic viral or bacterial infections such as hepatitis B and C or Helicobacter pylori gastritis (Cote et al., 1997; Suarez et al., 2006; Gucalp and Noy, 2009; Marcucci and Mele, 2011).

Finally, and - from the practical point of view - most importantly, it has been suggested that patients with a clonally unrelated second lymphoma should not receive aggressive treatment but be treated by standard first line therapy (Freedman et al., 2000). Obviously, the outcome of such treatment should be followed-up in large scale prospective clinical trials.

Classical Hodgkin lymphomas

cHL is a highly curable disease when treated with multimodal therapy (Rathore and Kadin, 2010). Unfortunately, approximately one third of patients will experience a relapse or do not respond to the initial therapy (Lohri et al., 1991; Ferme et al., 2002; Kobe et al., 2008). These patients are usually treated and potentially cured by more intensive therapy (Schmitz et al., 2002, 2005).

cHL is a neoplasm in which the neoplastic Hodgkin cells and Reed-Sternberg (HRRS) cells are highly outnumbered by reactive background cells. This morphological aspect has probably impaired the assessment of clonal relationships in relapsing cHL at the cellular level. In fact, cHL has for a long time been regarded a "reactive" process, denying its neoplastic nature (Re et al., 2005). Reports on clonal relationships in relapsing cHL have long been limited to individual case observations; only recently we systematically analyzed a series of 22 patients. In this study, we investigated whether the first and all subsequent manifestations of cHL in a patient were clonally related. HRSC were microdissected after CD30 staining using laser capture technique. We were able to show that some, but not all "relapses" were clonally related to the preceding lymphoma by BCR gene fragment length analysis. Two samples from recurrent tumors of the same patient could be successfully sequenced. These two late relapses were clonally unrelated by both BCR gene fragment length and sequencing analysis (Obermann et al., 2011).

Generally, a relationship in relapsing cHL can be examined by assessment of several aspects: morphology, i.e. histological subtype, immunohistochemical phenotyping, association with Epstein-Barr virus (EBV) and genetic analysis of HRSC. A change of morphology in relapsing cHL is a well-known finding; however, as it might be attributed to treatment, it has not been regarded as proof of or against "clonal" relationship of cHL recurrences (Amini et al., 2002). Immunophenotyping is probably not suitable to discriminate between clonally related and unrelated relapsing cHL since marker expression may vary between individual HRSC even within a given case (Tzankov et al., 2003). EBV association has been used to assess clonal relationship in recurrent cHL (Amini et al., 2002; Weiss et al., 1988). Correlation between EBV status in primary and recurrent cHL has been observed; however, change of EBV association can be documented in both clonally identical and unrelated cases (Obermann et al., 2011). Thus, a change of EBV association is probably not a good marker of clonal relationship in relapsing cHL, since virus infection may occur independently in unrelated neoplasms, not play a role at all in two related or unrelated neoplasms or get lost during progression of a clonally related tumor ("hit and run") (Ambinder, 2000; Tinguely et al., 2003). Therefore, analysis of HRSC at the molecular level seems to be the most appropriate albeit difficult way to assess the clonal relationship of relapsing cHL. Interestingly, the focus of molecular genetic research was on clonal relationship of cHL relapsing as NHL, e.g. SLL or DLBCL, or vice versa, i.e. clonal kinships in so called composite lymphomas (Tinguely et al., 2003; Fong et al., 2005; Kuppers et al., 2005; Schmitz et al., 2005) (Fig. 1). In one study applying genetic analyses to study clonal relationship of relapsing cHL, identically rearranged immunoglobulin

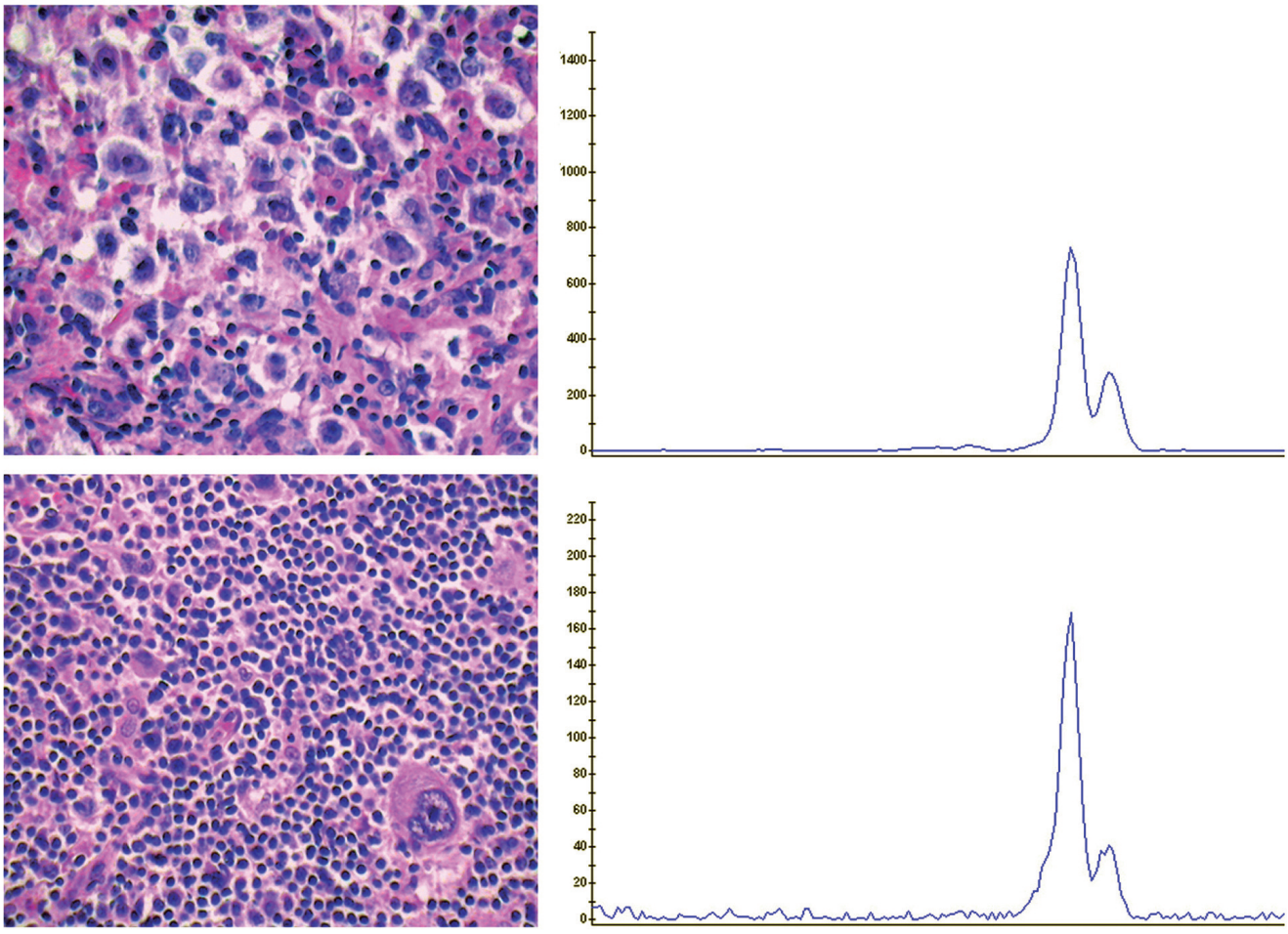

Fig. 1. Morphology and immunoglobulin heavy chain gene fragment length analysis in a patient presenting with a diffuse large B-cell lymphoma in 2000 (CD20+, CD79a+, PAX5+, CD45+, MUM1-, CD15-, CD30-, not shown), who recurred at the identical anatomic site as a classical Hodgkin lymphoma (CD20±, CD79a-, PAX5dim, CD45-, MUM1+, CD15±, CD30+, not shown) eight years later. The initial neoplasm is depicted on top, the second neoplasm on the bottom. Despite different morphology and phenotype, immunoglobulin heavy chain gene fragment length analysis suggests clonal relationship by identification of the same fragment lengths (94bp) in both lymphomas.

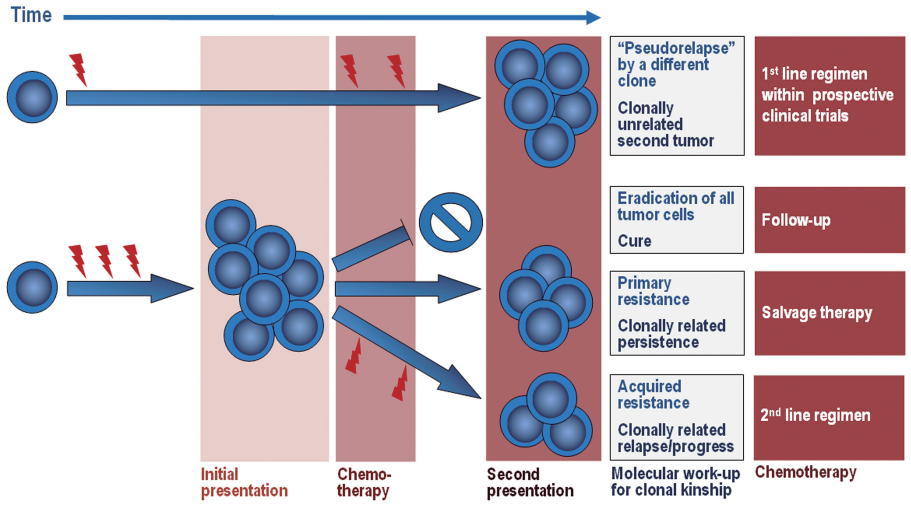

Fig. 2. Schematic of the possible scenarios and consequences of clinical lymphoma recurrences. Flashes indicate oncogenic ("gate keeper") mutations.

heavy (IGH)- or light chain genes were demonstrated in six of seven recurrent cases (Weiss et al., 1988). As already mentioned, in the largest study to date we were able to show the existence of clonally unrelated "relapsing" cHL by IGH fragment length analysis and in one case by IGH sequencing, both in early- (i.e. within one year) and late recurrences (i.e. after one year) (Obermann et al., 2011).

In summary, studies on clonal relationship in recurrent cHL are still few, but there is evidence that relapsing cHL are not always clonally related to the primary neoplasm. This finding is important from the practical point of view since testing of less aggressive treatment modalities in prospective trials for patients with clonally unrelated second presentations of cHL might be justifiable.

Concluding Remarks

The existence of "recurrences", which are biologically clonally unrelated "*de novo*" tumors of the same organ system, has been an established fact for a long time in solid organs. In contrast, recurring lymphoid neoplasms are in general considered "true" recurrences of the initial clone. However, this concept seems to be challenged now. There are three important issues to be considered.

First, the underlying mechanisms of relapsing lymphoid malignancies need to be more deeply investigated. Tumor stem cells giving rise to more than one tumor have been discovered in several solid neoplasms (Reya et al., 2001). The existence of tumor stem cells has been postulated and clonotypic B-cells with stem cell properties have been recently identified in cHL (Tinguely et al., 2003, Jones et al, 2009; Kuppers, 2009). A further fact, which supports the existence of "lymphoid tumor stem cells" is the occurrence of cHL and metachronous clonally related NHL in the same patient [summarized in (Amini and Enblad, 2003)]. From the practical point of view, strategies aiming at the elimination of such dormant cells with tumor stem cell properties might successfully prevent relapses.

Second, both genetic and environmental factors might predispose individuals to develop a lymphoid neoplasm. If these factors persist, as will be obviously the case for a genetic predisposition or untreated infection, development of a second, clonally unrelated neoplasm might be the consequence. Again, from the practical point of view, strategies aiming at the elimination of such factors, which could more easily be the case for the environmental and infectious ones, might successfully prevent relapses.

Third, the existence of clonally unrelated second lymphoid tumors of the same type, e.g. ALL or cHL, might be of clinical importance, as relapses are usually treated more aggressively than primary neoplasms with a significant treatment-related morbidity. This aspect can only be addressed by prospective studies evaluating the outcome in large numbers of patients with relapsing lymphomas, who are thoroughly investigated to prove a clonally (un-)related secondary neoplasm using up-to-date molecular techniques. The ongoing development and availability of novel techniques such as array comparative genomic hybridization and next generation sequencing might soon help to prove without doubt the different clonal origin of neoplasms, which are still indistinguishable.

In the future we suggest a line of action, which is depicted in Figure 2. In case of a recurrent lymphoid neoplasm a work-up to assess, whether this recurrence is a true relapse of the original neoplasm should be considered. If a relationship can be demonstrated, second line or salvage therapy according to the current treatment guidelines seems to be prudent. However, if this "relapse" is identified as a clonally unrelated novel malignancy the patient might be treated within prospective clinical trials to assess the adequate treatment. Thus, prospective clinical trials addressing the outcomes and the proper therapies in relapsing lymphoid malignancies according to the presence or absence of clonal relationship to the initial neoplasms are warranted.

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