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EDITORIAL

Sex as decisive variable in lymphoid neoplasms—an update

The sex of a patient is a strong clinical variable in many malignancies, among which lymphoid neoplasms feature quite prominently. Ignored for a long time, the recognition of the fact that there are sex disparities in incidence, disease course, and outcome has increasingly led to the inclusion of the variable sex in study design, data acquisition and analyses, and reporting. However, there still is a great lack of information as to how and why sex plays a role in lymphoid cancers.

The immune system is inherently different between men and women, the genetic basis translating into disparities in, among other aspects, lymphocyte pools, cytokine and chemokine production, and antibody response intensities. In particular, hormones shape development and functioning of the immune system and influence the functional activity of immune cells and responses, which also result in the sex-specific prevalence for infectious and autoimmune diseases, respectively.[1,2] As malignancies originating from immune cells, chronic inflammatory and infectious conditions have been hypothesized and shown to cause the formation and outgrowth of pre-neoplastic cells which may develop into lymphoid neoplasms.[3] For chronic lymphocytic leukaemia (CLL), chronic antigenic stimulation has strongly been implicated for leukaemogenesis based on the high frequency of quasi-identical B-cell receptors (BCR) in unrelated patients.[4] Furthermore, the role of hormones *per se* has been discussed for development and course of lymphoid malignancies.[5] Information on hormones and hormone profiles in lymphoid malignancies, however, is scarce. In CLL patients, the hormone profiles of male and female patients were significantly altered compared with sex-matched healthy individuals, for some hormones this was associated with clinical stage and treatment-free survival (TFS).[6,7] Such a hormonal shift would consequently point towards a potential role for the corresponding receptors for development and/or course of the disease. In this respect, hormone receptors have been detected not only on healthy but also malignant blood cells,[8-11] some of which were found to be overexpressed and of prognostic value, thus suggesting some degree of functional relevance.[8,10,11]

The male to female ratio seen in many lymphoid neoplasms, including CLL, at diagnosis is 2 : 1, and is preceded by a similar incidence in monoclonal B-cell lymphocytosis, the CLL precursor condition, where men also have a higher risk to develop the malignancy.[12] This ratio has been observed in other ethnic and for most age groups,[13,14] the ratio may become more equal in patients over 70 years of age.[15]

As one of the causes for the sex disparities observed in cancer incidence and survival, the sex chromosomes have been implicated. A study by Dunford and colleagues (2017), carried out in mostly solid but also lymphoid tumours, found sex-specific loss-of-function mutations in and, consequently, differential expression of several genes on the sex chromosomes.[16] However, the genes reported in this study only occur at very low frequencies in CLL and appear to be of limited importance for development and disease course.[17] Also loss of the sex chromosomes can be found at regular albeit low frequencies in CLL, however, they do not show differences between women and men.[18] In addition, sex-specific differential DNA methylation has been reported, some autosomal but the majority on the sex chromosomes. These differences translated into different expression levels for the affected genes in male and female CLL patients, with as yet unknown consequences.[19]

Clinically, sex-specific differences are subtle, and sex-specific bias with regard to genetic aberrations is rarely reported, and often information is conflicting. On the one hand, for diffuse large B-cell lymphoma (DLBCL) and CLL no differences have been observed for the clinically relevant chromosomal changes between men and women.[7,20] On the other hand, Cantú (2013) found skewed male-to-female ratios for standard CLL FISH probes (M : F 1.5), and the loss of *ATM* gene was higher in men compared with women [odds ratio (OR) 1.7045, $P = 0.0049$].[21] Studies on gene variants or single nucleotide polymorphisms (SNPs) for various genes showed variable associations of gene mutations with the sex of patients and did not find sex-specific functional consequences on response or survival.[22-26] Most often, sex-specific disparities are found and reported for the mutational status of the immunoglobulin heavy chain variable region (IgHV) gene. Sex was differently distributed between the mutated (M) and unmutated (UM) subgroups, with men more likely showing UM IgHV ($P = 0.009$), in addition to having a higher prevalence in the UM stereotyped BCR subsets (M : F between 1 and 4.4, $P = 0.001$, compared with 0.8 to 2.0 for the M stereotyped BCR subsets, $P = 0.03$).[4,27,28] Furthermore, epigenetic silencing of the NfκB gene *RELB* through heterochromatinization has been found in aggressive subsets of male and female CLL patients, but was most pronounced in males and led to reduced response to drugs *in vitro*.[29] The differential distribution of women and men seen in patients with chronic inflammatory or infectious conditions is reflected in lymphoid malignancies. Subgroups of leukaemia and

lymphoma patients that also suffer from autoimmune diseases are shifted to females (55% of CLL and 87.05% of non-Hodgkin's lymphoma patients),[30,31] with CLL patients suffering from concomitant chronic inflammatory conditions also being more likely to have bad risk markers.[30]

Most obvious, male and female CLL patients display differences for TFS and/or overall survival (OS). Hence, sex was included as a variable in several risk scores and prognostic indices for risk stratification, particularly in early stage patients with male sex constituting a risk variable for OS and/or TFS.[32-34] Inclusion of sex was based on statistically significant survival differences between men and women seen both in univariate and multivariate analyses, hazard ratio (HR) for male sex varying from 1.3 to 1.67 in these studies. Independent of risk scores, male sex still conferred shorter OS and/or TFS, the survival difference surpassing 1 year or more in some studies.[7,35,36] However, such differences were not observed in all investigations, similar survival probabilities between men and women underline the variability of observations.[37-39]

Information on response to treatment by sex is difficult to discern; in many cases, this information is not provided at all. Also, due to the many therapeutic regimens and combinations and small sizes of study cohorts, comparison of response based on a patient's sex often is conflicting. Thus, for treatment of CLL patients with fludarabine + cyclophosphamide (FC), male sex was found to be a risk factor for OS, not for progression-free survival (PFS) (for female patients: HR for OS 0.72, $P = 0.04$; HR for PFS 0.82, $P = 0.15$),[23] but also was reported to be associated with PFS, not OS (for female patients: HR for PFS 0.66, $P = 0.03$; HR for OS not listed).[40] In mantle cell lymphoma (MCL), lenalidomide had higher response rates in women with 5/7 women responding compared with 3/19 men ($P = 0.02$),[41] such a sex difference was not observed in DLBCL (17/65 females versus 22/65 males, $P = 1.0$) and CLL patients (HR males, 0.717 and HR females, 0.697).[42,43]

The addition of antibodies to chemotherapy and for maintenance in lymphoid malignancies drastically improved the outcome for both sexes. Rituximab (R), a first-generation IgG1 antibody, showed higher response rates and longer survival in male and female patients with CLL, the HRs for female and male patients were between 0.4 and 0.7 in the rituximab-containing arms.[44-47] Ofatumumab, a second-generation IgG1 antibody with higher binding affinity than rituximab, when added to chlorambucil (CLB) led to longer PFS in women and men with CLL, both favouring the antibody-containing arm with no differences between the sexes.[48] Alemtuzumab (A) added to FC prolonged the PFS in males compared with FC alone (HR FCA versus FC for males 0.66, for females 0.68), when added to FC + rituximab (FCR) women had longer median PFS than men (38 versus 32 months), but these differences were not significant between male and female CLL patients.[49,50]

However, sex-specific differences still were observed for response and survival in lymphoid neoplasms. In DLBCL, chemoimmunotherapy conferred better outcomes for women compared with men, with predicted worse PFS for male patients compared with females (HR 3.4; $P = 0.008$) and a 4-year survival rate in women of 75% versus 60% in men ($P = 0.013$).[51,52] In follicular lymphoma, males had inferior PFS under obinutuzumab + chemotherapy (4-year survival for women 68% versus 52% in men; $P = 0.036$).[52,53] In CLL, the addition of rituximab to chemotherapy improved the outcome of both sexes, but being male still was an independent predictor for OS and TFS with women having better outcome (male HR for OS 1.4 and for TFS 1.23).[54] Al-Sawaf (2017) reported sex-specific differences in relation to response for FCR, bendamustine + rituximab (BR) (FCR and BR PFS 60 months for females, 49 months for males; $P = 0.008$), and CLB + rituximab (CLBR) (18 months for women versus 14 months for men; $P = 0.008$), although not for CLB + obinutuzumab (no difference in PFS).[55] Studying the effects of cyclophosphamide + hydroxydaunorubicin + oncovin + prednisone (CHOP) +/− alemtuzumab for peripheral T-cell lymphoma showed male sex still to be an independent risk factor for event-free survival, PFS, and OS with no real difference between the two therapeutic arms (male HR being 2.5, 2.5, and 2.6, respectively, $P < 0.001$).[56]

In particular, the sex-specific difference in response and survival under rituximab-containing chemotherapy puzzled clinicians and scientists.[51,52] With the observation of differences in serum concentrations and clearance rates[57-59] came the realization that the immune system handles antibodies differently depending on sex. While the variable fragment antigen binding (Fab) region of an antibody binds the antigen, or the targeted molecule, the constant fragment or receptor (Fc) region binds to the cellular Fcgamma-receptors (FcγRs) which mediate and regulate effector functions, such as antibody-dependent cellular cytotoxicity or antibody-dependent cellular phagocytosis.[60,61] Signalling is dependent not only on the ratio of activating and suppressing FcγRs bound by an antibody, but also by the binding affinities to specific FcγRs, which in turn depend on the conformational state of the Fc region, mostly determined by N-linked glycosylation of Asn297. In addition, modifications of specific carbohydrates by *N*-acetylglucosamine, and the galactosylation, sialylation, and fucosylation of residues, and also functional polymorphisms determine the binding affinities of an antibody to the FcγRs.[61] Importantly, Fc region modifications vary both with age and sex.[60,62] Whereas changes not only seem to be more pronounced in women than in men, the differences associated with age also differ between the sexes.[62] The higher clearance rates observed for rituximab in men resulted in lower serum concentrations and consequently lower antibody levels in males compared with females. Median area under the curve in men was 81% of that found in women, and clearance rates of elderly females amounted to 8.5 ml/h compared with 10.6 ml/h in males,[57,63] which, in addition, were dependent on age and weight.[59,64] The sex-specific adjustment of rituximab doses for therapy led to the optimization of response and outcome in men, with HR for PFS changing from previously 1.6 to 0.6 and for OS from previously 1.4 to 0.8.[65] Similar to rituximab, obinutuzumab

levels were also dependent on sex and body weight,[53,66] with lower exposure in male and high-weight patients. In addition, obinutuzumab levels were dependent on FcγR polymorphisms.[53]

The lesson learned from rituximab was that, subsequently, novel antibodies were particularly evaluated for differences in serum levels and clearance rates between men and women. Thus, lower ofatumumab levels were observed in women (11.5% lower volume of central compartment) although sex was not a differentiating variable for response and survival.[67] Similarly, while sex-specific differences in pharmacokinetics were observed for obinutuzumab, men again exhibited higher clearance rates, these were moderate and not considered to be of clinical relevance.[66] Furthermore, a difference in PFS was observed between obinutuzumab + bendamustine versus obinutuzumab + CHOP/cyclophosphamide + vincristine + predisone. The variable exposure to obinutuzumab had no influence on PFS when combined with bendamustine; in contrast, adjusting antibody doses in the CHOP/cyclophosphamide + vincristine + predisone arm led to increased PFS,[53] indicating that other factors, for instance resistances to chemotherapeutic agents or disease biology, still appear to be of importance.[53] For the antibody—drug conjugate brentuximab vedotin, when used for various lymphoid malignancies, no differences between men and women have been reported.[68-70] This may be attributed to the directly delivered cytotoxic drug that kills the target cells independent of immune effector functions, thereby circumventing sex-dependent effects.

Also for immune checkpoint inhibitors (ICIs), sex-specific differences were observed with regard to pharmacokinetics and pharmacodynamics with trough levels differing between female and male patients, although not significantly. These, again, were considered to be moderate and of no relevance clinically.[71,72] ICIs improved survival of both sexes. In solid tumours, the reduced risk of death under ICI treatment was 0.73 for males and 0.77 for females ($P < 0.001$ for both sexes).[73] The benefit for OS for patients receiving ICI immunotherapy was HR 0.75 for men and 0.79 for women, with no difference of relative benefit for patients of different sex.[74] In addition, sex-dependent differences for programmed cell death protein 1/programmed death-ligand 1 (PD-1/PD-L1) versus cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibody regimens were reported. While PD-1/PDL-1 antibodies conferred similar improvement of outcome for both women and men, anti-CTLA-4 treatment appeared to be more effective in men, with a male HR for OS of 0.65 versus 0.79 for females ($P = 0.078$),[75] or men showing longer OS under anti-CTLA-4 antibody treatment with an HR of 0.77 ($P = 0.012$) compared with a female HR of 0.89 ($P = 0.162$).[73] Similar for PFS, the male HR was 0.67 ($P < 0.001$) compared with 0.77 ($P = 0.1$) for females.[73] These data, however, are heterogeneous and varied between solid tumour entities, making interpretation difficult or not feasible. Information for lymphoid malignancies, for which ICI therapy is being tested,[76,77] in this respect is lacking.

Finally, first data on CAR-T-cell treatments also suggest an advantage for women receiving CAR-T cells (overall response rates 58% for women versus 48% for men, which was not significant),[78] however, more information is required to determine any real sex-specific differences for this therapy.

In contrast to chemoimmunotherapy and immunotherapy, differences between women and men under therapy disappeared with the introduction of targeting drugs. While pharmacokinetics still were found to be different between the sexes, women showing 26% lower clearance rates of the Bruton's tyrosine kinase inhibitor CC-292 (spebrutinib) compared with men, this difference was negligible when considering the overall variability of clearance rates in the study cohort and did not lead to significant differences in overall response rates.[79] The Bruton's tyrosine kinase inhibitor ibrutinib, when compared with previous standard of care (including FC, FCR, CLB, bendamustine, rituximab, CHOP, and dexamethasone + high-dose ara-C + platinol) drastically reduced the higher male risk for PFS and OS (female HR for PFS 0.826; $P = 0.506$, female HR for OS 0.761; $P = 0.0424$).[80] Likewise, comparing ibrutinib + rituximab with FCR showed better response rates in the ibrutinib + rituximab arm independent of sex (HR 0.3 for women and 0.4 for men, respectively, compared with FCR).[81] Similar observations were reported also in other studies.[82,83] The spleen tyrosine kinase inhibitor entospletinib [objective response rates (ORR) 0.68 for male versus 0.46 for female patients], the BCL2 inhibitor venetoclax (similar rates of minimal residual disease), and the phosphoinositide 3-kinase (PI3K) inhibitor idelalisib (ORR 0.55 for males versus 0.6 for females) all displayed no sex-specific differences in response or survival.[84-86]

The difference in mode of action between therapeutic agents, inhibitors directly interacting with cellular molecules or antibody—drug conjugates directly delivering cytotoxic agents, compared with those antibodies that bind to surface molecules eliciting cellular responses, bypasses those functions that are inherently different between men and women, thereby taking sex-specific immune effects out of the equation. The increasing number of inhibitors due to investigations of mutational changes in pathways relevant to disease entities, but also the development of engineered antibodies, may overcome differences in outcome between men and women suffering from lymphoid malignancies and provide a large step forward for personalized patient care. Nevertheless, there still is a fraction of patients who develop resistances and display intolerances towards these drugs, the fall-back strategy for which will tentatively remain conventional chemoimmunotherapeutic and chemotherapeutic regimens, with their known disparities in response due to patient sex.

In order to assess a possible functional role of steroid hormone signalling for lymphoid neoplasms, selectively blocking molecules were used to interfere with hormone signalling that led to decreased survival and increased apoptosis of malignant cells *in vitro*, and reduced tumour mass *in vivo*.[10,87-91] The observation that interference with

the androgen receptor-reduced proliferation of MCL cells *in vitro* independent of sex,[10] subsequently was explored in a clinical trial using the androgen receptor antagonist enzalutamide (ClinicalTrials.gov Identifier: NCT02489123). The study, however, has been discontinued due to low response rates. The only patient still on treatment was the only female patient who had been showing disease control for over 24 months.[92] The data suggest, nonetheless, a possible benefit of AR-axis interference, and further studies are required to elucidate potential synergistic effects that may arise from blocking not only androgen but also other hormone signalling axes in combination with anti-cancer drugs.

Differences in drug metabolism in men and women, which are key to the variance in response,[93] are rarely mentioned and/or discussed in depth for lymphoid malignancies.[67,94] Studies investigating the sex-specific role of the immune system in the context of immune therapies are still underrepresented. Mostly, drug levels, clearance rates, and exposure times are being reported in relation to response to evaluate the safety and efficacy of a drug. These parameters are only a small fraction of sex-specific differences known to exist encompassing drug absorption (determined by gastric and hepatic enzymes, transporter proteins, and hepatic and renal handling of drugs and their metabolites), drug distribution (dependent on body fat composition and cardiac output), drug metabolism (involving hepatic and extra-hepatic sites, cytochrome P450 enzymes and phase II metabolic reactions), and drug elimination via kidneys, liver, or lung. All these aspects not only differ dependent on height, weight, body surface area, and body composition, but of course are dependent on sex including sex hormone levels.[93,95] Among phase II reaction enzymes, the UDP-glucuronosyltransferases (UGTs) feature quite prominently. Primarily responsible for steroid hormone metabolism, the enzymes belonging to this gene family glucuronidate not only steroid hormones but also xenobiotics, and thus inactivate the metabolized molecules, among them a number of drugs used in chemotherapy.[96] In particular, UGT2B17 was found to confer bad prognosis when overexpressed in CLL.[97,98] In addition, UGT2B17 overexpression was associated with significantly shorter TFS in women with CLL but not in male patients.[7] All UGTs are known for their high interindividual variation based on copy number variations, polymorphisms, and drug-induced expression, and, in addition, seem to be governed by alternative and/or additional forms of regulation.[99] Recently, it was shown that several of these enzymes were induced upon drug incubation of CLL cells *in vitro* leading to increased glucuronidation and inactivation of drugs, which included both chemotherapeutic and targeting agents.[99] The clinical consequences still have to be studied.

CONCLUSION

Sex as a decisive variable in lymphoid cancers has been well recognized for quite some time, the reasons behind these differences are still largely unknown. The enhanced interest in the dissection of differences between male and female patients has provided some information, particularly with regard to response to therapy and outcome. However, studies of biological, molecular, and translational aspects with reference to sex still are extremely rare. This includes the investigation of sex differences in the functioning of the immune system and immune responses in the context of lymphoid malignancies as diseases originating from this system. It appears particularly important considering the differences displayed by immunotherapies compared with targeting drugs that underlines the role of immune cells for this group of neoplasms. Most important would be the systematic and rigorous inclusion and reporting of the variable sex in study design, data acquisition, and analysis to better understand the sex-related nature of lymphoid malignancies in order to optimize personalized medicine approaches.

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