



ASH highlights 2019: “aggressive B-cell lymphoma”

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Summary Despite its significant cure rate, diffuse large B-cell lymphoma (DLBCL) remains a tumor entity of unmet medical need. The 2019 meeting of the American Society of Hematology (ASH) in Orlando, Florida, presented numerous directions, whereby clinicians may expect practice-changing innovations soon or in the near future. In this ASH highlight feature on “aggressive B-cell lymphoma”, a selection of prominent findings will be summarized. Targeted therapeutics try to meet the needs of patients subgroups that would benefit, and novel immune oncology agents now represent established treatment principles for relapsed/refractory (R/R) DLBCL. Moreover, intense research efforts have been undertaken to identify biomarkers of response. Imaging-based and molecular diagnostic tools are becoming increasingly instrumental in appraising individual risk prior to the first treatment encounter and in the early phase of induction therapy. Genomic analyses of circulating tumor DNA conducted in the peripheral blood has gained attention in terms of assigning patients to dedicated tumor subtypes, monitoring their molecular tumor burden in the course of the disease, and steering personalized treatment extensions in the near future.

Keywords CAR T-cells · DLBCL · Liquid biopsy · Ibrutinib · Molecular subgroups

Introduction

Will the dilemma of negative large randomized phase III trials in the diffuse large B-cell lymphoma (DLBCL) arena continue? Solidifying evidence in emerging areas, less “major breakthroughs” but numerous highlights of practice-impacting developments in the field of aggressive lymphoma were reported at the annual meeting of the American Society of Hematology (ASH) in Orlando, Florida, in December 2019. Besides T-cell-based therapies, in particular the exploitation of molecular in-depth diagnostics bore the potential as real game-changers for DLBCL patients and their molecularly and clinically highly heterogeneous disease.

Small compounds: indications for lenalidomide or ibrutinib in the first-line arena?

Unfortunately, abstract number 352 (Oberic et al. [1]) added with the lenalidomide extension of the DLBCL chemo-immune induction standard just another negative phase III trial to the long list in this regard. After the negative report of the ROBUST trial—R-CHOP ± lenalidomide for non-GCB (germinal center B-cell)—at the Lugano meeting earlier in 2019 (Vitolo et al., *Hematol Oncol*, 2019 [2]), this abstract presented (at ASH) data from the SENIOR study by the French Lysa group, a trial conducted in the very elderly over 80 years of age receiving R-miniCHOP as chemo-immune backbone. Addition of the immunomodulatory agent proved to be more toxic but failed to detect an advantage for this SENIOR patient cohort, which was, unlike ROBUST, not pre-selected by cell-of-origin. Of note, a central problem of most previous phase III failures in DLBCL was the “dilution” of the enrolled cohort by too many patients with lower risk disease—thus, likely to be cured by

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the standard of care alone. Given the less favorable perspective of DLBCL patients older than 80 years in general, this may be less of a problem in the SENIOR trial, although these patients still achieve a 3-year overall survival (OS) of 50–60% without the lenalidomide extension. As in all other recently failed phase III trials in DLBCL, there is hope that flanking molecular analyses will provide insights into the specific characteristics of those patients that actually benefit from the addition of lenalidomide.

Irrespective of the formally negative phase III PHOENIX first-line DLBCL trial—R-CHOP±ibrutinib for non-GCB patients—reported at ASH the year before, abstract number 354 (Johnson et al. [3]), now presented an interesting subgroup analysis of this particular trial (Younes et al., J Clin Oncol, 2019 [4]). Specifically, the abstract aimed at elucidating the role of the BTK inhibitor ibrutinib in patients whose lymphomas exhibited combined high-level transcript expression of Myc and Bcl2, further confirmed by the respective protein expression *in situ*, called “double-expresser status” (DES), which, expectedly, was associated with poor outcome in the PHOENIX trial. Importantly, the addition of ibrutinib to R-CHOP equalized the DES-related inferior event-free survival (EFS) and OS across all ages. Patients below 60 years of age, for whom the previous global PHOENIX analysis unveiled a strong advantage, experienced, when scoring as DES, a particularly profound ibrutinib effect with respect to both EFS and OS—these 3-year marks were improved by around 25% each, a very remarkable result in such a hard-to-control DLBCL high-risk population.

Of interest is a second, somewhat hidden layer of the PHOENIX trial: a significant fraction, almost one third, of the non-GCB (by immunohistochemistry [IHC] as a mandatory entry criterion) patients actually turned out to be GCB by a transcriptome-based confirmatory test method. When focusing on the under-60 years of age subgroup, these patients benefitted similarly when compared to the aforementioned global younger cohort and the subgroup in this age class explicitly confirmed as ABC subtype. Since another “non-GCB” (by IHC) DLBCL trial (abstract number 761; Ramchandren et al. [5]), a phase II trial offering relapsed/refractory (R/R) DLBCL patients ibrutinib, lenalidomide and rituximab (“IR²”) revealed a fraction of double-hit lymphomas (DHL) in those that subsequently scored as GCB by transcriptome-based re-analysis, it would be of interest to learn whether those particularly poor-prognosis DHL were among the ibrutinib-benefitting DES patients in the PHOENIX subgroup analysis presented at ASH 2019. Unfortunately, this information was not available when the abstract was presented in oral format in 2019 in Orlando.

Interim PET-guided treatment de-escalation in newly diagnosed limited stage (I/II) DLBCL patients?

The profound biological heterogeneity across DLBCL cases underscores the need for better molecular classifiers, prognosticators and predictors at the time of initial diagnosis and highlights the clinical demand for early indicators of actual response, i.e. functional positron emission tomography (PET)-based imaging in particular. The CONSORT trial (NCTN S101), a SWOG-Intergroup study conducted in the United States (Abstract number 349, Persky et al. [6]), evaluated in newly diagnosed limited stage (I/II) DLBCL patients whether a PET-guided treatment de-escalation to only four cycles of R-CHOP instead of the regular six might be justifiable. An interim PET was carried out after three cycles of induction therapy (iPET3). If negative, as achieved by the vast majority of the patients, only one additional cycle of R-CHOP was administered. By contrast, the small group of iPET3-positive patients received an alternative consolidation strategy consisting of involved-field radiation plus ibrutinib plus tiuxetan, a β -ray-emitting Yttrium-90-labelled CD20 antibody, thereby achieving an outcome comparable with iPET3-negative patients. Given the large proportion of iPET3-negative patients, this study reflects more of a confirmation of the “FLYER” data presented at ASH 2018 by Dr. Viola Poeschel on behalf of the German high-grade lymphoma study group (Poeschel et al., Lancet, 2020, [7]). This—actually positive—phase III trial demonstrated that younger patients with stage I/II disease without bulk and without risk factors had an excellent outcome when treated with just four cycles of R-CHOP plus two additional rounds of R—with a 3-year PFS of 96%, a level (almost) also reached by the SWOG trial. Hence, the key message is that induction therapy limited to four cycles is the new sufficient standard of care for young patients with limited stage disease without risk factors. Whether or not an interim PET provides additional guidance in this low-risk group of younger DLBCL patients remains to be seen.

Novel genomic lymphoma subtypes: simplifying the complexity in clinical practice?

A central theme of the congress was abstract contributions with reference to the recently published genomic in-depth analyses of lymphoma samples from large DLBCL patient cohorts, which led to the classification of novel molecular “clusters” (Shipp lab; Chapuy et al., Nat. Med. 2018 [8]) or novel molecular subtypes (Staudt lab; Schmitz et al., New Engl. J. Med. 2018 [9]). In the expectation that these novel subgroups not only have prognostic or R-CHOP-predictive meaning, but also provide information to select differential targeted treatment options, it will be important to simplify the complex molecular des-

ignation of a given patient to such cluster/subtype classification systems in clinical practice. A systems-overarching algorithm based on a 55-gene classifier was introduced by abstract number 551 (Esfahani et al. [10]). A particular strength of this approach was its suitability for both lymphoma biopsies and liquid biopsies, i.e. the analysis of circulating tumor DNA (ctDNA) from peripheral blood plasma samples. Interestingly, liquid biopsies also proved to be instrumental for a cell-of-origin designation as GCB or activated B-cell (ABC) subtype at a highly concordant level with transcriptome-based lymphoma analyses (see also abstract number 490, Tabari et al. [11]). Moreover, the authors demonstrated how reliably ctDNA analyses conducted in liquid biopsies may actually detect prognostically relevant single-nucleotide variants (such as p53 mutations) or translocations (such as *myc* rearrangements). Moreover, those prominent tumor suppressor and oncogenic alterations were exploited for the quantitative estimation of subclone dynamics, including the burden of minimal residual disease, in the course of disease (see also abstract number 921 by Rushton et al. [12]). Equally interesting were complex studies that addressed the lymphoma microenvironment, thereby unveiling prognostic contributions of distinct normal bystander cell compositions in the micro-milieu independently of the above-mentioned lymphoma subtypes (abstract number 656 by Cerchetti et al., [13]). A similar strategy even linked so-called eco systems, complex groups of lymphoma and normal cell populations characterized by certain activity states, to long-term survival (abstract number 655 by Steen et al. [14]). In essence, some of those nucleic acid-based approaches may rapidly impact on clinical practice. As a perspective, the retrospective re-analysis of the numerous negative large-scale phase III “R-CHOP ± X” trials by simplified gene classifiers may unveil hitherto unknown but actually benefitting subgroups—and, thereby, might provide the basis for confirmatory prospective trials in those genetically determined patient groups.

Next-generation bispecific T-cell engager: alternative or additional options in the context of CAR T-cells?

Of course, expectations were high regarding any ASH-reported news from the arena of cell-based lymphoma therapies. In addition to the more mature chimeric antigen receptor (CAR) T-cell data due to extended follow-up, which underscored the importance of complete remission (CR) with respect to lasting disease control (Lisocaptagene Maraleucel [TRANSCEND NHL001 trial]; abstract number 241 by Abramson et al. [15]) and demonstrated the relevance of an early steroid intervention to mitigate higher-grade cytokine release syndrome (CRS) and neurological events (NE) (Axicaptagene Ciloleucel [ZUMA-1 trial]; abstract number 243 by Topp et al.

[16]), promising developments emerged regarding bispecific T-cell-engaging antibodies (so-called BiTEs). A phase I/II trial investigating the CD3 x CD20-binding BiTE mosunetuzumab (with a half-life allowing a 3-week application cycle) in the setting of heavily pretreated R/R DLBCL patients yielded a 37% overall response rate, with CRs in more than half of the cases, and mostly of durable perspective. Remarkably, this magnitude was also seen in the (few) patients that previously received CAR T-cells; 2/8 mosunetuzumab patients exhibited a re-expansion of their CAR T-cells (abstract number 6 by Schuster et al. [17]). All-grade CRS and NE were noticed in 29 and 43% of the patients, respectively; grade 3/4 toxicities were mostly of hematological nature, with a neutropenia rate of 22%. Similar results were reported in ASH abstract number 762, referring to a phase I trial for REGN1979, another CD3 x CD20 BiTE that can be administered on a weekly basis: with an OR rate of 58% (11/19 patients, with eight of these in CR), half of the CAR T-cell-pre-exposed patients (6/12) responded to REGN1979, and 25% achieved CR (Bannerji et al. [18]).

Take home messages

- Ibrutinib as an addition to R-CHOP-based first-line therapy is effective in both younger DLBCL patients (<60 years of age) and those with “*Myc/Bcl2* double-expresser” lymphomas
- Tools to cross-interpret individual lymphoma data from different major DLBCL classification systems on novel genetic subtypes are available; the analysis of ctDNA from blood plasma (so-called liquid biopsy) may also be utilized to properly assign a patient’s lymphoma to these prognostically and potentially therapeutically relevant genomic subtypes
- Due to improved genetic engineering, CARs and BiTEs—chimeric antigen receptors and bispecific T-cell engager—have become more efficient and better manageable in the clinic, hence, will further add to the success story of T-cell-mediated treatment strategies

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