Precision Treatment of Distinct Molecular Subtypes of Diffuse Large B-cell Lymphoma: Ascribing Treatment Based on the Molecular Phenotype

Kieron Dunleavy, Mark Roschewski, and Wyndham H. Wilson

Abstract
Although diffuse large B-cell lymphoma (DLBCL), the most common type of non-Hodgkin lymphoma, was once considered to be a single disease, novel insights into its biology have revealed that it is molecularly heterogeneous. Technologies such as gene expression profiling have revealed that DLBCL consists of at least three distinct molecular diseases that have disparate outcomes following standard therapy. These subtypes arise from different stages of B-cell differentiation and are characterized by distinct oncogenic activation mechanisms. This knowledge has led to the investigation of strategies and novel agents that have selective activity within molecular subtypes and sets the stage for an era of precision medicine in DLBCL therapeutics, where therapy can be ascribed based on molecular phenotype. This work offers the chance of improving the curability of DLBCL, particularly in the activated B-cell subtype, where standard approaches are inadequate for a high proportion of patients.

See all articles in this CCR Focus section, "Paradigm Shifts in Lymphoma."

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Introduction
Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma diagnosed in the United States each year. Although the addition of rituximab to cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) improved curability of the disease, there remain a significant proportion of patients for whom standard therapy is ineffective (1). Over recent years, the availability of gene expression profiling and other high-resolution genetic technology has provided novel molecular insights into DLBCL and revolutionized our understanding of its biology (2–5). We now appreciate that this disease constitutes several molecular subtypes, originating from different stage of B-cell differentiation (3, 6–10). Most cases arise either from a germinal center B cell (GCB) or an activated B cell (ABC) that is blocked during plasmacytic differentiation. When these two subgroups were first identified, GCB DLBCL constituted 45% to 50% of cases—some DLBCL tumors did not fit into either GCB or ABC definitions and were called "unclassifiable." Later, another subtype called primary mediastinal B-cell lymphoma (PMBL) that makes up 10% of cases was also recognized. This new molecular taxonomy for DLBCL is important because distinct subtypes have disparate outcomes following standard therapy (11). This lays the foundation for testing new agents and novel strategies in distinct subtypes of DLBCL and investigating whether they have selective activity within these.

The applicability of gene expression profiling (GEP) and this new molecular taxonomy to clinical practice has been challenging, though, as GEP using microarrays on RNA derived from frozen tissue is not widely available and is expensive to perform. Therefore, many groups investigated the use of relatively inexpensive immunohistochemical methods and developed immunohistochemistry algorithms to predict cell of origin (12–14). While these techniques have been somewhat helpful, they have demonstrated varying degrees of concordance with microarray results, limiting their usefulness (15–18). Therefore, novel, more accurate assays to predict cell of origin are needed. Recently, quantitation of gene expression in formalin-fixed paraffin-embedded tissue (FFPET) was shown to be feasible in lymphoma cases, and the Lymphoma and Leukemia Molecular Profiling Project recently described a robust method for cell of origin assignment using a 20-gene assay (Lymph2Cx)—with this digital gene expression (NanoString)–based test, importantly, there was >95% concordance of cell of origin assignment between two laboratories (15, 19). The assignment of cell of origin by this assay also appeared more robust than by the widely used Hans algorithm (Fig. 1). This assay also has a rapid turnaround time of 36 hours, suggesting that it could be used for patient selection in prospective clinical studies and ultimately in the community for determination of upfront therapy, pending the results of ongoing studies.
All three subtypes of DLBCL are characterized by distinct genetic aberrations, though there is some overlap observed (Fig. 2). For example, the GCB subtype, which is most commonly encountered, is associated with markers of the germinal center such as CD10 as well as the BCL6 gene (20). The key molecular feature of the ABC
subtype is constitutive activation of the NF-κB pathway with high expression of NF-κB target genes. BCL2 is expressed by both the GCB and ABC subtypes—in the GCB subtype, its expression is typically associated with a t(14:18) translocation, whereas in the ABC subtype, its expression reflects NF-κB activation (6). These contrasting molecular features suggest distinct derivations of the GCB and ABC subtypes from different stages of B-cell differentiation. Importantly, following standard immunochemotherapy (R-CHOP), the outcome for patients with the ABC versus the GCB subtype appears to be inferior (11; Fig. 2).

Current Approaches to DLBCL

Most newly diagnosed patients with DLBCL receive rituximab in combination with a chemotherapy backbone consisting of CHOP. This backbone has been used since the early 1970s when doxorubicin was added to cyclophosphamide, vincristine, and prednisone (CVP), and CHOP became the first curative regimen in DLBCL, highlighting the critical role of anthracyclines. Later, in an attempt to improve upon the results with CHOP, subsequent studies focused on the empiric addition of drugs to the regimen. This did not improve survival, however, as evidenced in a pivotal randomized study comparing CHOP with second- and third-generation regimens, where there was no evidence of superiority (but higher toxicity) with the latter approaches (26). Later, other groups, such as The Deutsche Studiengruppe f"ur Hochmaligne Non-Hodgkin’s Lymphome (DSHNHL), also
attempted to improve upon the outcomes with CHOP. They carried out four-arm studies of CHOP, where they tested different schedules of the regimen (every 14 vs. every 21 days) with or without etoposide (CHOEP) in both older (>60 years) and younger (≤60 years) patients (27, 28). Although CHOEP-21 benefited patients <60 years and CHOP-14 patients >60 years, these survival gains did not remain significant with the addition of rituximab [following a study from Groupe d’Etudes des Lymphomes de l’Adulte (GELA) that showed a survival advantage in older patients treated with R-CHOP versus CHOP; refs. 27–31]. The RICOVER-60 study was a randomized comparison in elderly patients of 6 versus 8 cycles of CHOP-14, with or without rituximab (30). Although the DSHNHL found no significant differences in survival between the two groups, they concluded that R-CHOP-14 should be adapted as the new standard based on historical comparisons in this population (30). Subsequently, however, two randomized studies—one in all age groups (>18 years) and the other in older patients (>60 years)—showed no benefit of R-CHOP-14 over R-CHOP-21, and hence, the latter remains the standard (32, 33; Fig. 3).

Other researchers have investigated increased dose-intensity approaches as an alternative to R-CHOP. Rituximab with doxorubicin (Adriamycin), cyclophosphamide, vindesine, bleomycin, and prednisone (R-ACVBP) was compared with R-CHOP-21 in a randomized study performed by the GELA group, in patients under 60 years with an age-adjusted International Prognostic Index (IPI) score of 1 (34). Although the R-ACVBP arm demonstrated an improved progression-free survival (PFS; 87% vs. 73%), the significant hematologic toxicity of the regimen confines its use to younger patients, and it is not feasible for most (older) patients who have DLBCL. This restricts its potential to replace R-CHOP as the universal platform for this disease. Other intensive approaches, such as using autologous stem cell transplantation in the upfront setting, have been tried but they have never shown a clear benefit over R-CHOP alone and are associated with much higher toxicity (35). Another increased dose-intensity regimen is dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin with rituximab (DA-EPOCH-R; ref. 36). Following promising activity in NCI and Cancer and Leukemia Group B (CALGB) single-arm studies, a randomized study (that incorporated molecular profiling) comparing DA-EPOCH-R with R-CHOP recently completed accrual, and results are awaited (37).

**Treatment of GCB DLBCL**

This is the most common subtype of DLBCL and represents almost all cases (excluding PMBL) that are...
diagnosed in children, adolescents, and young adults (38). Though it appears to have a much better outcome compared with ABC DLBCL following standard therapy, approximately 30% of patients with GCB DLBCL do not achieve cure with R-CHOP (11). The BCL6 gene is a transcriptional repressor and has been shown to be a critical regulator of the germinal center with important roles in the regulation of apoptosis, lymphocyte activation, and the DNA damage response (39). Although up to 40% of GCB DLBCL cases harbor a BCL6 chromosomal translocation, deregulated BCL6 may also result from mutations not involving the BCL6 locus (20). Translocations and somatic mutations of BCL6 can augment the inhibitory effect of BCL-2 on the apoptotic stress response, resulting in tumor proliferation and treatment failure. This suggests that BCL6 is an important therapeutic target in GCB DLBCL (40).

Specific small-molecule inhibitors of BCL-6 are currently in development (40–42). One such inhibitor—called 79–6 complex—works by binding to the BCL6 BTB domain corepressor binding groove (41). Strategies such as histone deacetylation inhibition—to overcome the repressive effects of BCL6 on p53 and cell-cycle–inhibitory proteins—are also potentially interesting in DLBCL (43, 44). One recent study demonstrated that treatment of DLBCL cell lines with pan-deacetylone inhibitors in combination with niacinamide produced synergistic toxicity in GCB over ABC subtypes and led to acetylation of BCL6 and p53 (44). In a phase I proof-of-principle study, 24% of patients with relapsed lymphoma attained a response to vorinostat and niacinamide.

Cells in the germinal center are rapidly dividing and topoisomerase II dependent, and therefore strategies that target topoisomerase II are rational in GCB DLBCL. Agents such as etoposide can inhibit topoisomerase II via ubiquitin-mediated protein degradation and possibly transcriptional inhibition resulting in downregulation of BCL6 (45). This is interesting when one considers the improvement in event-free survival in younger patients when etoposide is added to CHOP (CHOEP vs. CHOP alone). Younger compared with older patients have a much higher proportion of GCB DLBCL, and this may explain the benefit of adding etoposide in this group (27, 28). Though any survival benefit of adding etoposide did not persist with the addition of rituximab to CHOP (R-CHOEP), the earlier results suggest that GCB DLBCL may be sensitive to strategies that incorporate topoisomerase inhibition (29). The DA-EPOCH-R regimen includes the topoisomerase II inhibitors etoposide and doxorubicin, and topoisomerase II inhibition is optimized by the continuous infusion of agents in addition to pharmacodynamic dosing. This ensures adequate steady-state concentrations that may be critical in tumor cell kill (36). Following DA-EPOCH-R in patients with DLBCL, the outcome of the GCB subtype was particularly promising—at a median follow-up of 5 years, event-free survival (EFS) ranged from 95% to 100% (46, 47).

The histone methyltransferase enhancer of Zeste homolog 2 (EZH2) are another interesting therapeutic target in GCB DLBCL (48–50). In GCB DLBCL, gain-of-function mutations in the H3K27 methyltransferase EZH2 are present in 25% of GCB DLBCL. Inhibitors of EZH2 are toxic to GCB cell lines and are currently in development and may be helpful in this subtype (48, 49).

Treating ABC DLBCL

ABC DLBCL is rarely diagnosed in children and younger patients and proportionally increases in incidence with advancing age. Results from many studies suggest that it is the subtype with the worst outcome following standard therapy, so novel approaches are particularly needed for these patients (11, 51). These tumors have constitutive activation of the NF-κB pathway that drives tumor proliferation and survival and confers chemotheraphy resistance. The NF-κB pathway is also important in marginal zone B-cell lymphomas, and Zucca and colleagues (52) discuss this in this CCR Focus edition. Early studies by Davis and colleagues (53) validated NF-κB as a therapeutic target in ABC DLBCL. In both GCB and ABC cell lines, an inhibitor of IκB kinase (which is critical for activation of NF-κB) was tested and showed differential activity within ABC cell lines. Subsequently, a clinical study was developed based on the hypothesis that inhibiting NF-κB in DLBCL might sensitize ABC (but not GCB) DLBCL to chemotherapy (54). The investigational agent in the clinical study was bortezomib, a proteasome inhibitor that prevents the degradation of phosphorylated IκBα in the proteasome, which leads to inhibition of NF-κB activity in ABC DLBCL cell lines in vitro. Bortezomib was tested in combination with anthracycline-based chemotherapy (DA-EPOCH) in relapsed and refractory DLBCL, and molecular subtype was determined (where possible by gene expression profiling) on study entry. Patients with the ABC versus the GCB subtype had a significantly superior overall response rate (83% vs. 13%; $P = 0.0004$) and median overall survival (OS; 10.8 vs. 3.4 months; $P = 0.0026$). The results of this study and others suggest that there is a basis for developing novel therapeutic strategies directed at individual molecular subtypes, and currently, randomized studies testing R-CHOP with or without bortezomib are under way in newly diagnosed patients with non–GCB DLBCL (Table 1; ref. 55).

Over the past few years, our understanding of various mechanisms of NF-κB activation in ABC DLBCL has evolved significantly, and this has paved the way for the development of several new classes of agents that target NF-κB. In particular, recent work has underlined the importance of chronic B-cell receptor (BCR) signaling as well as activating mutations in CARD11 and MYD88 in driving NF-κB (Fig. 4; refs. 56–59). As a result, several specific inhibitors of critical pathways that drive NF-κB activation are in development (60). An important step in the activation of NF-κB by BCR signaling is regulated by Bruton tyrosine kinase (BTK), and several specific inhibitors of BTK are now in clinical development. One of these—ibrutinib—selectively kills cell lines with chronic active BCR signaling. Ibrutinib covalently inhibits BTK and is
orally bioavailable (56). Recently, a multicenter study tested ibrutinib in 70 patients with relapsed and refractory DLBCL. Twenty-nine cases included had ABC DLBCL, 20 had GCB DLBCL, and 21 cases were “unclassifiable” (61). Interestingly, there was selective activity within the ABC group. Although the overall response rate was 23%, 41% of patients with ABC DLBCL responded compared with only 5% in the GCB group \( (P = 0.007) \); ABC patients also showed a trend toward better survival (than GCB patients; ref. 9; 76 vs. 3.35 months; \( P = 0.099 \)). This selective activity of ibrutinib within the ABC subtype supports the role of BCR signaling in the activation of ABC DLBCL but not GCB DLBCL (56). One very interesting component of this study was the mutational status analysis of individual tumors. When correlated with outcome, tumors with BCR and MYD88 mutations had a high response rate, whereas those with CARD11 mutations did not, highlighting the dominance of downstream signaling in the latter group (61). On the basis of the selective activity of ibrutinib in ABC DLBCL, a randomized study of R-CHOP versus R-CHOP with ibrutinib is under way in newly diagnosed patients with non–GCB DLBCL (Table 1). Several other inhibitors of BTK are also in development (62).

Several other kinase inhibitors that target ABC DLBCL are under investigation. Enzastaurin is an oral potent inhibitor of protein kinase C\( _{\beta} \), which is a serine/threonine kinase. It is amplified through the BCR signaling pathway and likely plays a critical role in NF-\( \kappa B \) activation. However, recently, a phase III study investigating its activity in the prevention of relapse in DLBCL was stopped early as disease-free survival was no better than it was with placebo in patients at high risk of relapse following rituximab-based chemotherapy. Fostamatinib, an Syk inhibitor, has shown activity across a wide range of lymphomas including DLBCL but has not demonstrated selective activity within ABC DLBCL (63). The PI3K/AKT/mTOR signaling pathway appears to be important in these tumors as evidenced by the fact that both temsirolimus and everolimus, which inhibit mTOR, have induced remissions over several different lymphoma types (64–66). The optimal targets of this pathway are unknown, but upstream molecules, such as AKT or PI3K, may be particularly promising. Idelalisib is a potent inhibitor of PI3K p110\( _{\delta} \) and results in the blockade of constitutive PI3K signaling \( \textit{in vitro} \). Although it is effective in indolent B-cell lymphomas, it has not shown activity in DLBCL so far (67, 68). MYD88 is another potentially important target in ABC DLBCL as it is mutated in approximately 30% of cases (58). It activates NF-\( \kappa B \) via a signaling cascade involving IRAK1 and IRAK4. IRAK4 activity is critical for the oncogenic effect of MYD88, and IRAK4 inhibitors have selective activity in ABC cell lines (58). These agents, therefore, represent another rational therapeutic strategy for ABC DLBCL.

Immunomodulatory agents such as lenalidomide are another interesting class to consider. Lenalidomide selectively kills ABC DLBCL cells \( \textit{in vitro} \) by augmenting IFN\( \beta \) production through its effects on IRF4 (69). It has selective activity in the ABC group as evidenced by a phase II study in relapsed and refractory DLBCL, in which the response rate was much higher in patients with ABC versus GCB DLBCL (55% compared with 9%; ref. 70). Lenalidomide has been safely combined with R-CHOP (R2-CHOP), and in two studies, the combination has demonstrated high efficacy in patients with newly diagnosed DLBCL (71, 72). In a recent report of 64 patients with DLBCL, there was no significant

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Abbreviations: A, doxorubicin (Adriamycin); B, bortezomib; I, ibrutinib; R2-CHOP, rituximab, lenalidomide (Revlimid), CHOP; Vc, bortezomib (Velcade).
difference in the 24-month PFS and OS of GCB versus non-GCB patients who received R2-CHOP (73). In contrast, PFS and OS of the non-GCB group were significantly inferior in a comparison control group who received R-CHOP. On the basis of these results, a randomized phase II study is under way in previously untreated patients.

**MYC, BCL2, and Double-Hit Lymphomas**

Approximately 10% of DLBCL cases harbor an MYC rearrangement, and this has been associated with an inferior outcome following R-CHOP chemotherapy (74–76). Cases that harbor an additional BCL2 (or BCL6) translocation have been termed “double-hit” lymphomas and have a particularly poor outcome following standard therapy (77). Most of these are of GCB derivation. At this time, optimal therapy for these diseases has not been defined and there is no definite role for upfront transplantation (78).

Recently, there has been much interest in so-called “double-expressor” lymphomas that have high protein expression of MYC and BCL2 but without translocations. These are usually of non-GCB origin, and like “double-hit” lymphomas also have a poor outcome following standard therapy (79, 80). On the basis of efficacy in Burkitt lymphoma, the DA-EPOCH-R regimen was retrospectively assessed in both MYC-rearranged and MYC-negative DLBCL, and there was no difference in outcome between the two groups (81–83). A multicenter prospective study is under way to test the regimen in MYC-rearranged DLBCL. Strategies in development to specifically target MYC include small-molecule inhibitors of the bromodomain and extraterminal domain family (BET) chromatin–associated proteins such as JQ1 and I-BET 151. Although they have shown preclinical activity in tumors harboring rearrangements of MYC, they also seem to be active in nontranslocated cancers with deregulation of MYC at the posttranscriptional level (84).

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**Figure 4.** Map of BCR and MYD88 signaling pathways and potential targets. Signaling through BCR leads to downstream activation of the NF-κB transcription factor, which is a driver pathway in ABC DLBCL. Signaling also activates the AKT/MTOR and MAP kinase pathways. Constitutive MYD88 signaling is an alternative pathway leading to NF-κB activation. Reprinted from ref. 69. Cancer Cell, Vol. 21, Yang Y, Shaffer AL 3rd, Emre NC, Ceribelli M, Zhang M, Wright G, et al., Exploiting synthetic lethality for the therapy of ABC diffuse large B cell lymphoma, p. 723–37. Copyright 2012, with permission from Elsevier.
MYC-driven lymphoma, Aurora kinase inhibitors are interesting agents and in development (85). BCL2 is expressed in both GCB and ABC DLBCLs. It is typically associated with a t(14:18) translocation in GCB DLBCL and is a marker of NF-κB activation in ABC DLBCL. The association between BCL2 overexpression and outcome is complex—although older studies suggested that it portended a poor prognosis, more recent studies have not found this. Several specific inhibitors of BCL2, such as navitoclax and ABT-199, are in development (86).

Treating PMBL

PMBL comprises 10% of DLBCL cases and is predominantly diagnosed in young females. It arises in the mediastinum and is derived from a thymic B cell (21). Although it is recognized as a subtype of DLBCL, it clinically and molecularly resembles nodular sclerosing Hodgkin lymphoma arising in the mediastinum. Its molecular profile is very different from either GCB or ABC DLBCL and is much closer to nodular sclerosing Hodgkin lymphoma, with which it shares a third of its genes (24).

Because of the rarity of PMBL, there has been a lack of prospective studies and therefore poor consensus on how best to approach its management (22). Early studies, which were performed by Italian groups, suggested that mediastinal radiotherapy was a critical component of curative therapy and it continues to be widely used. One early study that established this standard tested MACOP-B (methotrexate, leucovorin, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin) followed by consolidative radiation therapy. Although 66% of patients were gallium positive at the end of chemotherapy, this reduced to 19% after mediastinal radiation, suggesting that radiation was critical (87). Dose intensity has always been considered to be important in PMBL therapeutics, and given the close relationship of PMBL to nodular sclerosing Hodgkin lymphoma—where dose intensity is beneficial—this is not unexpected (88). Many retrospective studies assessed the role of dose intensity, including one where MACOP-B and VACOP-B (etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin) were compared with CHOP; the outcome in the CHOP group was inferior, suggesting a role for dose intensity in PMBL, and this was demonstrated in other studies (89–91). However, due to the rarity of PMBL, there have not been any prospective randomized studies of dose-intense versus conventional approaches.

Most studies have suggested a benefit to using rituximab in PMBL. In a subgroup analysis of the MabThera International Trial (MInT) that was confined to patients with PMBL, the additive benefit of rituximab in combination with CHOP-like regimens was assessed (92). Patients who received rituximab had a superior 3-year event-free survival (78% vs. 52% in the chemotherapy arm alone)—because of small numbers, an OS difference was not appreciated. Most patients in this analysis received preplanned mediastinal radiation which improved remission rates (93, 94). It is important to consider that the MInT study was confined to patients with a low IPI score (≤1) and therefore did not include the entire spectrum of patients with this disease. Other studies have evaluated R-CHOP in patients of all risk groups with the disease. One of these retrospectively evaluated 58 patients of all IPI groups treated with R-CHOP (followed by mediastinal radiation in 77% of responders; ref. 94). There was a high rate of primary induction failures (21%), and the overall PFS at 5 years was 68% (94). Another retrospective study evaluated R-CHOP followed by ifosfamide, cyclophosphamide, and etoposide without radiation and reported a PFS of 78% at 3 years (95). Recently, the International Extranodal Lymphoma Study Group reported a 5-year PFS rate of 86% in 125 patients with PMBL who received different immunochemotherapy regimens followed by radiation in the majority of cases (96).

Though combined modality treatment is very effective in PMBL, the addition of mediastinal radiation is clearly associated with significant long-term morbidities (97). The increased risk of breast cancer is particularly problematic. Although lower doses of radiation may reduce these risks, this has not been clearly demonstrated yet (98). In an attempt to develop a strategy that removed the need for radiation, an NCI study investigated the dose-adjusted EPOCH-R regimen without radiation in PMBL and included all risk groups of patients (37). In 51 patients, EFS and OS rates were 93% and 97%, respectively, at a median follow-up of 5 years, and consolidation mediastinal radiation was administered to just 2 patients (99). In 16 additional patients with PMBL who received the regimen at another center, EFS and OS were 100% without radiation. On the basis of these promising results, the approach is being tested by other groups, and an early report from a German pediatric/adolescent study demonstrated high efficacy without radiation (100). Future strategies in PMBL should continue to focus on reducing toxicity and testing rational and promising novel agents (101).

Conclusions

We are entering an era of precision treatment of distinct subtypes of DLBCL. Though once considered to be a single-disease entity, there is now recognition that DLBCL is clinically and molecularly heterogeneous and, importantly, distinct subtypes have disparate outcomes following standard therapy. One big challenge has been the ability to correctly diagnose molecular subtypes in the clinic, but recent studies have shown that quantitation of gene expression in FFPE is feasible with a very short turnaround time, suggesting broad applicability in the future. Recent studies have demonstrated that certain novel agents have differential activity within subtypes of DLBCL. There are now ongoing studies investigating distinct approaches within molecular subtypes of the disease. It is likely in the future that selection of upfront therapy for patients with DLBCL will be determined based on molecular phenotype.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.
References


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