Recent advances in the treatment of B-cell lymphoma

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Abstract

There have been unprecedented advances in the management of B-cell lymphoma in the last decade. These include staging, treatment, and bench observations.

Introduction and context

Significant changes in the staging, outcome, and management of B-cell lymphomas have occurred over the last decade. Monoclonal antibodies, unconjugated or conjugated to radioisotopes, that target lymphoma-specific surface markers have changed the natural history of B-cell lymphomas [1]. In 1993, the US Intergroup study demonstrated that the standard of care in diffuse large B-cell lymphoma (DLBCL) was cyclophosphamide, adriamycin, vincristine, and prednisone (CHOP) administered every 21 days (CHOP-21) for eight cycles [2]. Monoclonal antibody therapy in combination with chemotherapy (immunochemotherapy) improved the overall survival (OS) in DLBCL. Monoclonal antibody therapy has subsequently been used in other aggressive lymphomas as defined by the World Health Organization (WHO) classification [3]. The most studied antigen is a pan-B-cell antigen, CD20, which does not shed into the cytoplasm, internalize, or undergo significant modulation. Other B-cell antibodies and T-cell antibodies have entered the clinical arena. The WHO classification of lymphomas has been further modified and in 2008 a new classification will define more than 50 types of lymphoma [4]. Positron emission tomography (PET) scans have altered the clinical staging of patients.

Recent advances

Classification and staging

The new fourth edition of the WHO lymphoma classification further defines and differentiates non-Hodgkin lymphoma (NHL) [4]. Follicular lymphoma (FL) is defined as low-grade FL 1-2, intermediate-grade

FL 3A, and high-grade FL 3B, and there is no follicular grade 3 lymphoma with DLBCL. DLBCL categories now include T-cell-rich/histiocytic-rich large B-cell lymphoma, primary central nervous system, cutaneous B-cell, Epstein Barr virus (EBV)-associated, lymphomatoid granulomatosis, and other categories. Other aggressive lymphomas include B-cell lymphoma unclassified intermediate between Burkitt lymphoma and DLBCL, B-cell lymphoma intermediate between DLBCL and classical Hodgkin lymphoma, EBV-associated T-cell clonal lymphoproliferative disease, and anaplastic large-cell lymphoma, alk-1-negative, provisional category. These changes are the result of a vast and rapid accumulation of biology and clinicopathologic observations that are beyond the scope of this review.

Functional imaging with 18-fluoro-deoxyglucose PET (FDG-PET) has improved the accuracy of restaging evaluations after primary treatment for NHL. PET scanning after one to four cycles of chemotherapy is a sensitive indicator of tumor response and clinical outcome [5,6]. FDG-PET interpretations have been incorporated into clinical trial response criteria and treatment guidelines [7,8]. Response criteria for interim analysis are not the same as those validated for the end of treatment analysis, and PET is recommended 3 weeks after chemotherapy [7]. Positive PET scan lesions should be rebiopsied [9].

Treatment

Diffuse large B-cell lymphoma

Rituximab is a chimeric anti-CD20 human immunoglobulin G1 monoclonal antibody approved for the

treatment of DLBCL. Phase III studies reported an improved progression-free survival (PFS) and OS, which led to US Food and Drug Administration approval for patients with new DLBCL in 2006. In the landmark randomized prospective trial of R-CHOP versus CHOP in elderly patients primarily with DLBCL, the Groupe d'Étude des Lymphomes de l'Adulte (GELA) reported superior PFS and OS with R-CHOP with rituximab administered as rituximab on day one of each of eight CHOP cycles compared with CHOP [9,10]. Three hundred and ninety-nine patients 60 to 80 years old were randomly assigned to receive eight cycles of CHOP or R-CHOP (rituximab and CHOP). The 7-year PFS rates were 52% for R-CHOP and 29% for CHOP ($P < 0.0001$), the DFS rates were 66% for R-CHOP and 42% for CHOP ($P = 0.0001$), and the OS rates were 53% for R-CHOP and 36% for CHOP ($P = 0.0004$) [10]. In the US Intergroup Eastern Cooperative Oncology Group 4494/Cancer and Leukemia Group B (CALGB) 9793 trial with a median follow-up of 3.5 years, the estimated 2-year failure-free survival (FFS) rates after second random assignment were 77% for R-CHOP followed by observation, 79% for R-CHOP + maintenance rituximab (MR), 74% CHOP + MR, and 45% for CHOP followed by observation ($P < 0.001$) [11]. A secondary analysis was performed to elucidate the effects of induction treatment without MR. In this analysis, R-CHOP alone significantly decreased the risk of treatment failure compared with CHOP alone [hazard ratio (HR) = 0.64, 95% confidence interval (CI), 0.47 to 0.85; $P = 0.003$] with estimated 3-year FFS rates of 52% for R-CHOP and 39% for CHOP. In addition, OS was longer after R-CHOP induction alone (HR = 0.72, 95% CI 0.52 to 1.00; $P = 0.05$) with estimated 3-year OS rates of 67% for R-CHOP and 58% for CHOP. The 3-year FFS (R-CHOP 53% and 52% and CHOP 35% and 35%, respectively), OS (R-CHOP 62% and 67% and CHOP 51% and 58%, respectively), and respective FFS HR (0.58 and 0.64) and OS HR (0.72 and 0.72) were similar in the GELA and US Intergroup trials despite differences in high-risk International Prognostic Index (IPI) characteristics (R-CHOP 12% versus 23% and CHOP 15% versus 27%, respectively). The continued use of MR after R-CHOP failed to demonstrate a benefit at the time of the initial report or in follow-up at 5.5 years [12]. At 7 years, 48% of the deaths were secondary to lymphoma [13]. A Canadian population study confirmed the OS observations of R-CHOP over CHOP from the GELA and the US Intergroup trials [14]. The Mabthera International Trial (MinT) was a randomized international trial of 824 young patients from 18 countries and 172 participating institutions of six cycles of CHOP-like chemotherapy plus rituximab (413 patients, 355 evaluable for response) versus CHOP-like therapy (411 patients, 350 evaluable for response) alone

in young patients with good-prognosis (favorable and intermediate-risk) DLBCL with additional radiation therapy to bulky and extranodal disease [15]. Patients had zero or one adverse IPI factor. At a median follow-up of 34 months (range of 0.03 to 61), patients treated with chemotherapy and rituximab had an increased 3-year OS of 93% (90 to 95%) versus 84% (80 to 88%) with a difference between the groups of 9% (3 to 13%; $P = 0.0001$). The efficacy was confirmed in a retrospective population-based study [14].

Two studies demonstrated that standard-dose CHOP administered every 14 days (CHOP-14) results in a longer OS than CHOP-21 in patients 18 to 60 years old or 61 to 75 years old [16,17]. Phase II studies evaluating R-CHOP-14 have been reported [18–20]. An international ongoing study of R-CHOP-21 versus R-CHOP-14 will further address the question of every-2-week versus every-3-week R-CHOP by the French GELA and British National Cancer Research Institute.

Future trials are evaluating other approaches. Epratuzumab has been combined with R-CHOP-21 in the treatment of previously untreated DLBCL [21]. Epratuzumab is a humanized monoclonal immunoglobulin G1 antibody directed against the B-cell-specific antigen CD22 that is expressed by pre-B cells and mature normal B cells and is expressed in approximately 85% of DLBCL. In the initial feasibility study of 15 patients with DLBCL, the complete response (CR) rate was 67% and the partial response (PR) rate was 20%. The 2-year PFS and OS rates were 86% and 86%, respectively. The North Central Cancer Treatment Group reported an expanded phase II study of this regimen [22]. The infusion regimen DA-EPOCH-R (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab) has been developed at the National Cancer Institute (Bethesda, MD, USA) and preliminary data demonstrate that this regimen is effective among all biomarker subgroups [23]. The CALGB has initiated a phase III randomized study of R-CHOP-21 versus DA-EPOCH-R, incorporating molecular profiling and pharmacogenomics to determine whether DA-EPOCH-R represents a treatment advance. The US Intergroup study (S9704) is assessing the role of HDT and autologous transplantation after five cycles of R-CHOP versus completing eight total cycles of R-CHOP-21 and no transplant in younger patients with high-intermediate or high-risk disease.

New approaches to patients who have relapsed/refractory disease include the small molecules. Lenalidomide (Revlimid®) is an immunomodulatory drug that is being evaluated at the phase II level. In 21 patients with relapsed/refractory DLBCL, there were three CRs and two

PRs with seven patients with stable disease (SD) [24]. mTOR (mammalian target of rapamycin) is a key kinase that regulates cell cycle progression from G₁ to S phase. In an initial phase II study, there were one CR and five PRs with a 50% overall response rate (ORR) in patients with aggressive lymphoma after a median of seven cycles of treatment [25].

The standard of care after relapse after DLBCL is salvage therapy followed by high-dose chemotherapy with stem cell transplant [26]. In phase II trials, the addition of rituximab to salvage chemotherapy regimens may improve the ORR with ICE (ifosfamide, carboplatin, and etoposide), EPOCH, and DHAP (dexamethasone, cisplatin, and cytarabine) [27,28]. The Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL) and other trials are addressing the questions of the most optimal salvage regimens prior to stem cell transplant.

Primary mediastinal large B-cell lymphoma

Primary mediastinal large B-cell lymphoma is a subset of DLBCL with distinct clinical characteristics that include a mediastinal presentation in young females, unique pathologic features that include sclerosis, and a unique molecular gene expression signature with a more favorable outcome than DLBCL. The 5-year OS in patients less than 65 years old treated with CHOP-R was 81% and the impact of rituximab was not determined [29]. In a non-randomized series of patients, 26 patients were treated with DA-EPOCH and 26 patients were treated with DA-EPOCH-R [30]. Rituximab was associated with a significantly improved event-free survival ($P = 0.038$) and OS ($P = 0.023$).

Burkitt lymphoma

Burkitt lymphoma is a rare lymphoma. Dose-adjusted (DA) chemotherapy that is adjusted by pharmacokinetics, DA-EPOCH-R, was administered over the course of 4 days for six cycles in 13 HIV-negative patients and three to six cycles in six HIV-positive patients and resulted in a CR rate of 100% in 19 patients [31]. At a median follow-up of 28 months, all patients were alive and in remission.

Post-transplant lymphoproliferative disorders

The most common post-transplant lymphoproliferative disorder (PTLD) is the monomorphic DLBCL, which is highly associated with immunosuppressive treatment and EBV. In a phase II study of rituximab, the ORR was 44% with a CR rate of 35% with few relapses and 65% of patients had delayed-onset PTLD, which likely accounted for the lower response rate [32].

Follicular lymphoma

Before the immunochemotherapy era in follicular lymphoma, therapeutic approaches improved the duration of response and only marginally improved OS. There are now four trials that have reported an improved OS with the addition of rituximab to CVP (cyclophosphamide, vincristine, and prednisone), CHOP, MCP (mitoxantrone, chlorambucil, and prednisolone), and CHVP+I (CHOP + interferon) [33–37]. Radioimmunoconjugate therapy with ¹³¹I-tositumomab in patients with limited bone marrow involvement produced a 59% 5-year PFS in the first-line treatment of patients with FL [38].

Other studies

Ongoing studies are evaluating surrogate markers for the cell of origin microarray signature [39]. However, at this time, 20 to 40% of patients are not defined by standard immunohistochemical markers [39]. Host germ-line immune gene single-nucleotide polymorphisms are predictive of survival in FL and DLBCL [40,41]. Future strategies will define biologically defined prognostic factors in FL that are not available at this time.

Implications for clinical practice

The new WHO classification will be incorporated into clinical trials. This will necessitate incorporation of this classification into routine pathology and clinical practice. PET scans now predict outcome and are incorporated into clinical trials in DLBCL and other lymphomas to evaluate the most optimal timing of a repeat PET scan following the initiation of treatment. The utility of PET scans in follicular and low-grade lymphoma is under further evaluation. Rituximab has now improved the OS in DLBCL and FL for the first time in over 25 years. Ongoing studies are further refining the incorporation of rituximab into treatment regimens. By December 2007, there were over 17 international randomized phase III studies in DLBCL [42]. Critical ongoing trials in FL include the US Intergroup trial comparing R-CHOP versus CHOP followed by tositumomab, and the GELA PRIMA (Primary Rituximab and Maintenance) study evaluating the role of 2 years of MR therapy after a rituximab chemotherapy induction regimen will further define the new treatment paradigms. New oral agents are demonstrating significant activity in B-cell lymphomas with different mechanisms of action. These provide patients with new opportunities for therapeutic interventions following relapse. New observations in the biology of the disease will change treatment approaches.

In conclusion, targeted therapies with monoclonal antibodies and monoclonal antibodies conjugated to radioimmunoconjugates have altered the natural history of

NHL. Future directions in targeted therapy to the cell membrane and cellular pathways will continue to alter the natural history of the multiple histologies of B-cell NHL.

Abbreviations

CALGB, Cancer and Leukemia Group B; CHOP, cyclophosphamide, adriamycin, vincristine, and prednisone; CI, confidence interval; CR, complete response; DA-EPOCH-R, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein Barr virus; EPOCH, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; FDG-PET, 18-fluoro-deoxyglucose positron emission tomography; FFS, failure-free survival; FL, follicular lymphoma; GELA, Groupe d'Etude des Lymphomes de l'Adulte; HR, hazard ratio; IPI, International Prognostic Index; MR, maintenance rituximab; NHL, non-Hodgkin lymphoma; ORR, overall response rate; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; PR, partial response; PTLD, post-transplant lymphoproliferative disorder; R-CHOP, rituximab-cyclophosphamide, adriamycin, vincristine, and prednisone; WHO, World Health Organization.

Competing interests

The author declares that he has no competing interests.

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