BLOOD RESEARCH
Volume 52 · Number 1 · March 2017
https://doi.org/10.5045/br.2017.52.1.3

Perspective

The Consortium for Improving Survival of Lymphoma (CISL): recent achievements and future perspective

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Received on January 15, 2017; Accepted on March 7, 2017

Introduction

The Consortium for Improving Survival of Lymphoma (CISL) of the Korean Society of Hematology Lymphoma Working Party is a multicenter collaborative study group performing prospective clinical studies for lymphoma patients and retrospective analyses. Since 2006, the CISL has performed >35 prospective clinical trials and >30 retrospective studies to investigate the clinical and pathological features of lymphoma subtypes and the outcomes of new therapeutic modalities. The year 2016 is the 10th anniversary of the CISL, and this report aims to commemorate its progress during the past 10 years. The CISL previously reported its achievements between 2006 and 2012, including 32 publications as of the end of 2012 [1]. Herein, we summarize clinical studies conducted by the CISL from 2013 to 2015.

Retrospective studies

Bone marrow karyotyping in diffuse large B-cell lymphoma: The CISL evaluated the cytogenetic aberrations in the bone marrow (BM) of diffuse large B-cell lymphoma (DLBCL) patients [2] in a retrospective multicenter analysis of 1,585 newly diagnosed DLBCL patients. Isolated cytogenetic aberrations without histologic involvement were found in 21 patients (1.3%). Two or more cytogenetic abnormalities were associated with lower overall survival (OS). Isolated cytogenetic aberrations in the BM can indicate BM involvement, and cytogenetic evaluation of BM improves staging accuracy in addition to providing prognostic information for DLBCL patients.

Autologous stem cell mobilization: We compared various chemo-mobilization regimens, e.g. high-dose (HD) cyclophosphamide, HD etoposide, and platinum-based chemotherapies [3]. HD etoposide mobilized a significantly higher number of CD34+ cells than the other 2 approaches, and the successful mobilization rate was also significantly higher with HD etoposide.

Waldeyer's ring lymphoma: The clinical features of Waldeyer's ring (WR) NHL patients were analyzed [4]. DLBCL was the most common pathologic subtype, followed by peripheral T-cell lymphoma (PTCL) and extranodal NK/T-cell lymphoma (ENKTL). Age ≥62 years, T-cell subtype, and failure to achieve a complete response (CR) were significant risk factors.

Mantle cell lymphoma: We retrospectively analyzed 131 mantle cell lymphoma (MCL) patients [5]. Their median age was 63 years (range, 26-78 years; male, 77.9%). One hundred five patients had stage III or IV disease. Fifty-two patients were categorized as high- or high-intermediate risk by the International Prognostic Index (IPI). Eighteen

patients were in the high-risk group by the simplified MCL-IPI (MIPI). Extranodal involvement was found in 69.5%, BM in 41.2%, and gastrointestinal tract in 35.1%. R-CHOP was a frequent first-line treatment (41.2%). Two-year OS was 64.7%, while the event-free survival (EFS) was 39.7%. The simplified MIPI was significantly associated with OS.

Intraocular lymphoma: Twenty intraocular (IOL) patients were studied [6]. Four patients were diagnosed with IOL alone. Two patients later developed central nervous system (CNS) involvement. Nine patients developed CNS lesions before the onset of IOL. Five patients had simultaneous onset in the eye and CNS. Intravitreal injection of methotrexate and/or various combinations of systemic chemotherapy with or without radiotherapy were administered. The median progression-free survival (PFS) was 19.7 months and 3-year OS was 75.1%.

Lymphoblastic lymphoma: We evaluated the efficacy of hyper-CVAD induction and stem cell transplantation (SCT) consolidation in 49 lymphoblastic lymphoma (LBL) patients [7]. The overall response rate (ORR) was 79%: 73% CR and 6% partial response (PR). Among responders, 24 patients underwent autologous (N=16) or allogeneic SCT (N=8). Their 3-year OS and PFS were 76% and 78%, respectively. Fifteen patients without SCT consolidation showed poorer PFS. Hyper-CVAD is effective for remission induction in LBL, and SCT consolidation produced better clinical outcomes.

Burkitt lymphoma: We evaluated the outcomes of 43 adult Burkitt lymphoma (BL) or Burkitt-like lymphoma patients with no human immunodeficiency virus infection who were treated with a rituximab plus hyper-CVAD (R-hyper-CVAD) regimen [8]. The 2-year EFS and OS were 70.9% and 81.4%, respectively. R-hyper-CVAD resulted in excellent outcomes.

Sinonasal DLBCL: We evaluated primary sinonasal DLBCL patients treated with R-CHOP [9]. Fifty-nine patients received R-CHOP alone, whereas 21 were followed by involved field radiotherapy. In patients with stage I–II disease, no difference was found in the response rate and OS between the two groups. Among 11 patients with relapses, the most common type was local (n=8), with a CNS relapse in 1. Patients with primary sinonasal DLBCL treated with R-CHOP have a low CNS relapse rate and better OS compared to previous studies that did not use rituximab.

Marginal zone lymphoma: We analyzed 210 localized stage marginal zone lymphoma (MZL) patients (stage I: 180, stage II: 30) to explore the role of additional chemotherapy [10]. Twenty-eight patients received additional chemotherapy. In the local treatment and additional chemotherapy group, the median PFS was 147 and 103 months, and the OS was 188 and 137 months, respectively. Localized stage MZL has a good clinical course and is well controlled with local treatment modality without additional chemotherapy.

Prospective studies

Radioimmunotherapy: We investigated repeated ^{131}I-rituximab in B-cell lymphoma patients [11]. Thirty-one patients with relapsed or refractory (RR) B cell lymphoma received ^{131}I-rituximab at 4 week intervals. Repeated radioimmunotherapy (RIT) yielded two-fold increases in the response rate (68%) and in the median response duration (8.6 months). This approach also induced a favorable response in cases of aggressive histology.

PTCL phase 1 study: A phase I study of everolimus was performed as combination chemotherapy in PTCL [12]. Fifteen newly diagnosed stage III/IV PTCL patients were enrolled. The recommended dose of everolimus for combination chemotherapy was 5 mg. All evaluable patients achieved a response (8 CR and 6 PR). We concluded that everolimus (5 mg) can be safely combined with CHOP, leading to a feasible and effective regimen for PTCL.

Nasal ENKTL: We conducted a phase II trial of concurrent

Table 1. Published reports of the CISL trials according to lymphoma subtype and study type.

Entity		Prospective				Retrospective	Total
		1st line	Salvage	Cohort	Subtotal		
NHL	DLBCL	3	5		8	6	14
	MCL					1	1
	MZL	2			2	11	13
	ENKTL	2			2	2	4
	T-cell	3	2		5	2	7
	LBL/BL					3	3
	Others					4	4
HL						1	1
ASCT			1		1	1	2
Total					18	31	49

Abbreviations: NHL, non-Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; ENKTL, extranodal NK/T cell lymphoma; T-cell, T-cell lymphoma; LBL, lymphoblastic lymphoma; BL, Burkitt lymphoma; HL, Hodgkin lymphoma; ASCT, autologous stem cell transplantation; CISL, Consortium for Improving Survival of Lymphoma.

chemoradiotherapy (CCRT) followed by 2 cycles of VIDL for 30 patients with stages IE or IIE nasal ENKTL [13]. CCRT yielded a 90% ORR (CR: 20 patients); however, 2 patients developed distant disease progression. VIDL chemotherapy had a final 87% CR rate. The 5-year PFS and OS were 60% and 73%, respectively.

DLBCL: We tried 4 doses of weekly rituximab (375 mg/m^2) consolidation after 4 cycles of R-CHOP-21 in DLBCL patients aged ≥70 years [14]. The median age was 76 years (range, 70-89 yrs). Of 51 patients, 41 completed the planned rituximab consolidation and the ORR was 78.4% (CR, 74.5%). Two-year PFS and OS were 63.9% and 68.7%, respectively. No serious toxicities were reported.

RR PTCL: We investigated the gemcitabine, dexamethasone, and cisplatin (GDP) regimen for RR PTCLs [15]. Patients could proceed to autologous stem cell transplan-

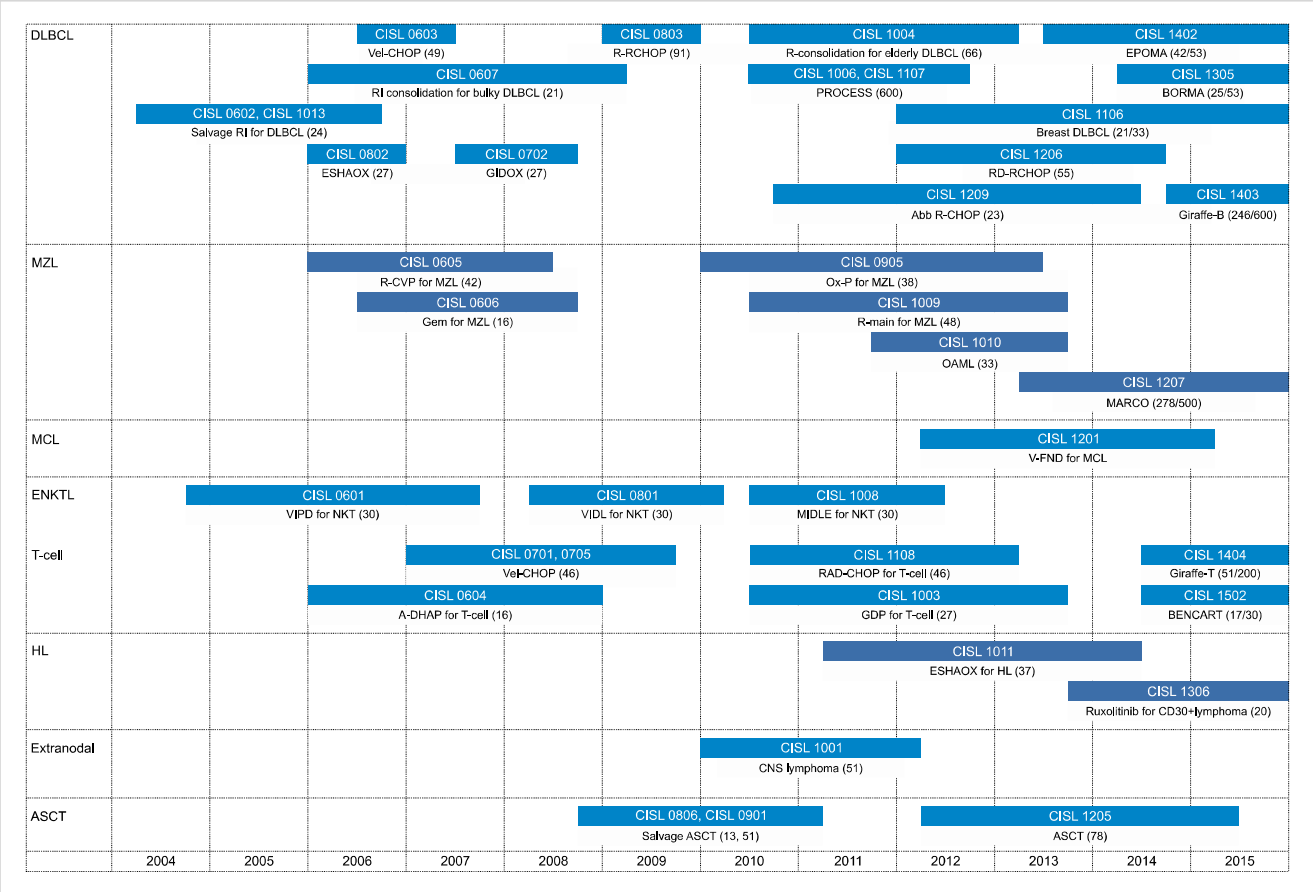

Fig. 1. Chronological flow of prospective Consortium for Improving Survival of Lymphoma studies.
Abbreviations: DLBCL, diffuse large B-cell lymphoma; MZL, marginal zone lymphoma; MCL, mantle cell lymphoma; ENKTL, extranodal NK/T cell lymphoma; HL, Hodgkin lymphoma; ASCT, autologous stem cell transplantation. CISL 0601, concurrent chemo-radiotherapy (CCRT) and weekly cisplatin followed by VIPD (etoposide, ifosfamide, cisplatin and dexamethasone); CISL 0602, radioimmunotherapy with 131I-rituximab; CISL 0603, bortezomib plus CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) every 2 weeks; CISL 0604, alemtuzumab plus and DHAP (dexamethasone, high-dose cytarabine and cisplatin); CISL 0605, rituximab (R) plus CVP (cyclophosphamide, vincristine and prednisolone); CISL 0606, gemcitabine single agent; CISL 0607, yttrium-90 ibritumomab tiuxetan consolidation following rituximab plus CHOP; CISL 0701, bortezomib plus CHOP; CISL 0702, GIDOX (gemcitabine, ifosfamide, dexamethasone and oxaliplatin); CISL 0801, CCRT followed by VIDL (etoposide, ifosfamide, dexamethasone and L-asparaginase) with risk-based application of ASCT; CISL 0802, ESHAOX (etoposide, methylprednisolone, high-dose cytarabine and oxaliplatin); CISL 0803, intensified 1st cycle R plus 8 cycles of R-CHOP, CISL 0806 and 0901, busulfan, melphalan and etoposide as conditioning; CISL 0905, Ox-P (oxaliplatin and prednisolone); CISL 1001, high-dose methotrexate induction followed by alternative high-dose methotrexate and high-dose cytarabine combination consolidation; CISL 1003, GDP (gemcitabine, dexamethasone and cisplatin); CISL 1004, R augmentation following R-CHOP induction; CISL 1006 and 1107, prospective cohort study with risk-adapted CNS and bone marrow evaluation; CISL 1008, CCRT followed by MIDLE (methotrexate, ifosfamide, dexamethasone, L-asparaginase and etoposide); CISL 1009, R-CVP followed by R maintenance; CISL 1010, R-CVP; CISL 1011, ESHAOX (etoposide, methylprednisolone, high-dose cytarabine and oxaliplatin); CISL 1106, R-CHOP and prophylactic intrathecal methotrexate; CISL 1108, everolimus plus CHOP; CISL 1201, vorinostat plus fludarabine, mitoxantrone and dexamethasone; CISL 1205, comparison intravenous busulfan, melphalan and etoposide versus intravenous busulfan, cyclophosphamide and etoposide as conditioning regimen; CISL 1206, R plus reduced dose CHOP for elderly; CISL 1305, phase II: bortezomib for maintenance in high-risk DLBCL; CISL 1306, pilot study: ruxolitinib in relapsed or refractory HL and primary mediastinal large B-cell lymphoma of high risk; CISL 1402, phase II, erythropoietin for anemia caused by chemotherapy in DLBCL; CISL 1403, prospective cohort registry of DLBCL; CISL 1404, prospective cohort study of peripheral T-cell lymphoma; CISL 1502, phase II, bendamustine, carboplatin and dexamethasone for refractory or relapsed peripheral T-cell lymphoma.

tation (ASCT) after 4 cycles of GDP or receive up to 6 treatment cycles. The diagnoses were PTCL-not otherwise specified in 14 and angioimmunoblastic T-cell lymphoma in 4. Twelve patients had a CR and 6 had a PR. Four patients proceeded to ASCT, and 3 patients achieved a CR. The median PFS was 9.3 months. GDP is a highly effective and optimal salvage regimen for RR PTCLs.

Future perspectives

By its 10th anniversary, the CISL has reported 18 prospective and 31 retrospective studies (Table 1). The CISL has 8 on-going prospective trials as of January 2016. The CISL has been conducting clinical studies in collaboration with specialists such as pathologists, radiologists, radiotherapists, and physicians of diagnostic laboratories and nuclear medicine (Fig. 1). Going forward, the CISL will focus on providing invaluable evidence to improve the clinical course of lymphoma patients through collaboration with international lymphoma study groups.

Acknowledgements

We are grateful for the patients' dedication to the clinical trials of CISL. We also appreciate the efforts of the CISL members, especially the clinical research coordinators.

Author's Disclosure of Potential Conflict of Interest

The author has no potential conflict of interest relevant to this article.

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