Background: Survival of patients with high-risk diffuse large B-cell lymphoma (DLBCL) is suboptimal, and the risk of central nervous system (CNS) progression is relatively high. We investigated the efficacy of dose-dense chemotherapy and systemic CNS prophylaxis in two completed Nordic trials including patients less than 65 years with high-risk DLBCL. We combined individual patient data from these studies to compare clinical outcome and prognostic factors in patients treated with CNS prophylaxis given in the beginning (CHIC) vs at the end (CRY-04) of therapy.

Patients and Methods: Inclusion criteria were age 18-65 years, primary DLBCL or grade 3 follicular lymphoma without signs of CNS involvement, WHO performance score 0-3, age-adjusted International Prognostic Index (aIPI 2-3) and/or involvement of anatomical sites associated with an increased risk for CNS recurrence (e.g. testis, facial sinuses, orbita). In CRY-04, six courses of R-CHOEP14 were followed by HD-Mtx and HD-Ara-C. In CHIC, treatment consisted of two courses of HD-Mtx in combination with R-CHOEP14, followed by four courses of R-CHOEP14 and one course of R-HD-AraC. In addition, liposomal Ara-C was administered intrathecally at courses 1, 3 and 5. Primary endpoints were failure free survival (FFS; disease progression, discontinuation of protocolled therapy due to toxicity, death from any cause) at 3 years and CNS progression rate at 1.5 years. Secondary endpoints included progression-free survival (PFS; disease progression or death from any cause) and overall survival (OS) at 3 years.

Results: Among 303 patients enrolled in the trials (CRY-04, n = 160 and CHIC, n = 143), 295 (CRY-04, n = 154 and CHIC, n = 139) met inclusion criteria and were evaluable for baseline characteristics and primary end points. Median age (54 and 56 years, p = 0.222), male/female ratio, stage and aIPI scores were comparable in the two cohorts. Three-year FFS was 63% in CRY-04 and 77% in CHIC (p = 0.018) after a median follow-up of 5 and 3 years, respectively. Cumulative incidence rates of CNS progression were 5.0% and 2.4% (p = 0.22), and 3-year OS 80% and 86% (p = 0.508), respectively. Treatment in the CHIC reduced the risk of systemic progression (aIPI adjusted RR = 0.484, 95%CI 0.300-0.782, p = 0.003). PFS benefit with CHIC vs CRY-04 was observed across pre-specified subgroups, and particularly in patients <60 years old (p = 0.007), with low proliferation index (Ki67 expression <75%, p = 0.029), and BCL2 positivity (p = 0.006). In the subsets of patients with available PET data, Deauville score 5 at the end of treatment was associated with increased rate of progression and death in both trials (p = 0.012). Only one out of 17 biopsies from PET positive lesions (DS 3-5) contained vital lymphoma tissue.

Conclusions: Our results derived from trial data with homogenous treatment support the use of HD-Mtx in the beginning rather than at the end of therapy. Superior outcome seems to be primarily due to better systemic control of the disease. In addition, number of CNS recurrences is reduced.

Keywords: CNS prophylaxis; diffuse large B-cell lymphoma (DLBCL); immunochemotherapy

INFECTIONS AND THERAPY-ASSOCIATED DEATHS IN ELDERLY PATIENTS WITH DLBCL UNDERGOING R-CHOP IMMUNOCHEMOTHERAPY

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Background: To study if anti-infective prophylaxis with aciclovir and cotrimoxazole is effective in preventing infections in pts. receiving R-CHOP, we compared infections and treatment-related deaths in two prospective DSHNHL trials with different anti-infective strategies.

Methods: 61- to 80-year-old pts. in RICOVER-60 study [Pfreundschuh et al; Lancet Oncol 2008; 9:105-116] received 6 or 8 cycles of CHOP-14 with or without 8 applications of rituximab. Anti-infective prophylaxis consisted of ciprofloxacin (500 mg/d) during days of severe leukocytopenia (<1000/mm³). In OPTIMAL > 60, pts. were randomized to 6xCHOP-14 or 6xCHLIP-14 (conventional substituted by liposomal vincristine [2 m²/m³, uncapped]) in combination with rituximab, 8 applications q 2 weeks or 12 applications between days -4 and 238 in a 2 × 2 factorial design. In OPTIMAL > 60, anti-infective prophylaxis consisted of cotrimoxazole (2 double-strength doses twice every week p.o.) and aciclovir (4 × 400 mg/d p.o.) in addition to ciprofloxacin.

Results: In RICOVER-60, grade 3-4 infections in 232 patients (IPI = 1 and bulky disease or IPI > 1) receiving 6xCHOP-14 + 8R were 6% (76/1200) per cycle and 28% (60/218) per patient. OPTIMAL > 60 pts. were older (70 vs 68 years) and had more IPI = 3 (33% vs 29%) and IPI = 4.5 (34% vs 23%) compared to RICOVER-60. With intensified anti-infective prophylaxis in OPTIMAL > 60, there were no differences with respect to infections between the 4 treatment arms. Despite the considerably less favourable demographics of the OPTIMAL > 60 study, grade 3-4 infections were 4% (83/1987) per cycle and 18% (64/365 pts. with toxicity documentation) per patient, significantly less than in RICOVER-60 (per cycle: p = 0.007; per patient: p = 0.004). Even more importantly, treatment-related deaths (defined as all non-lymphoma associated deaths during and within 2 months after the end of chemotherapy) went down from 15/232 (7%) in RICOVER-60 to 7/385 (2%) in OPTIMAL > 60 (p = 0.003).

ANTI-INFECTIVE PROPHYLAXIS WITH ACICLOVIR AND COTRIMOXAZOLE SIGNIFICANTLY REDUCES THE RATE OF INFECTIONS AND THERAPY-ASSOCIATED DEATHS IN ELDERLY PATIENTS WITH DLBCL UNDERGOING R-CHOP IMMUNOCHEMOTHERAPY
Conclusion: Anti-infective prophylaxis with cotrimoxazole and aciclovir in addition to ciprofloxazine significantly reduced the rates of severe infections and treatment-related deaths in elderly patients receiving R-CHOP supporting the use of this anti-infective strategy in all DLBCL patients receiving R-CHOP.

Keywords: diffuse large B-cell lymphoma (DLBCL); immunochemotherapy; R-CHOP

204 FREQUENCY OF PERFORATION & IMPACT OF BOWEL REST IN AGGRESSIVE NON-HODGKIN LYMPHOMA WITH GASTROINTESTINAL INVOLVEMENT: AN INTERNATIONAL, MULTI-CENTER RETROSPECTIVE STUDY


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Introduction: The gastrointestinal (GI) tract is involved in 10-15% of patients with newly diagnosed non-Hodgkin lymphoma (NHL) and can lead to perforation, peritonitis and death. Some physicians advocate admission for the first cycle of chemotherapy to facilitate early recognition and rapid surgical intervention. Others also employ bowel rest and prescribe total parenteral nutrition (TPN) to reduce peritoneal contamination in the event of perforation. However, it is unclear if these measures are effective.

Methods: We performed a multi-centre, retrospective analysis of patients with newly diagnosed aggressive NHL with GI involvement defined by either tissue biopsy or imaging between 1st January 2006 and 1st January 2016. Two centers employed bowel rest as a routine measure, while two did not. The Kaplan-Meier method was used to measure time from diagnosis to perforation and death or last follow-up. Univariate and multivariate analysis of factors associated with perforation and survival was performed using Cox regression.

Results: We identified 419 patients, 204 (49%) treated as outpatients and 215 (51%) as inpatients. Of inpatients, 106 (49%) received bowel rest; 109 (51%) did not. After a median follow-up of 3.6 years (range 0.1-11.9), 41 (9.8%) perforated; 28 (68%) at presentation or prior to chemotherapy. Excluding these, the median time to perforation was 28 days (2-877). Diffuse large B-cell lymphoma accounted for 85% of patients (357), high-grade B-cell lymphoma 3% (13), Burkitt lymphoma 5% (21), peripheral T-cell lymphoma 2% (9) and enteropathy associated T-cell lymphoma (EATL) 4% (16). There were one case each of plasmablastic lymphoma and anaplastic large cell lymphoma (0.4%).
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