R-ICE (利妥昔单抗-异环磷酰胺-卡铂-依托泊苷)联合来那度胺(R2-ICE)在首次复发/原发性难治弥漫性大 B 细胞淋巴瘤(DLBCL)患者中的 I/II 期研究

Phase I/II study of R-ICE (rituximab-ifosfamide-carboplatin-etoposide) with lenalidomide (R2-ICE) in patients with first-relapse/primary refractory diffuse large B-cell lymphoma (DLBCL) in academic and community cancer research united (ACCRU) network.

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背景：一线治疗后复发/难治性弥漫性大 B 细胞淋巴瘤(DLBCL)（R/R DLBCL）患者对挽救性免疫化疗的缓解仍不令人满意。来那度胺（Len）单药治疗在复发/难治性 DLBCL 中具有显著的活性。在 1b 期研究中，第 1 至 7 天给予来那度胺（Len）联合 RICE 方案（利妥昔单抗+异环磷酰胺-卡铂-依托泊苷）被证明是可行的（Feldman T 等，BJH，2014）。我们进一步进行了 I / II 期研究，以评估对于符合干细胞移植条件的 R / R-DLBCL 患者，在 RICE 中联用 Len（延长至 14 天）（R2-ICE）的安全性和有效性。

方法：设计 I 期研究中，采用标准队列 3 + 3 设计，以确定与 RICE 联

用 Len 的最大耐受剂量。每天 15 mg 和 20 mg 逐步增加剂量，至 14 天。常规强制性给予阿司匹林和生长因子预防性支持治疗。治疗 2 个周期后，通过 PET / CT 扫描评估疗效；在 HDC / SCT 之前，获得缓解的患者可再给予另外 1-2 个周期的 R2-ICE 疗程。估计 R/R DLBCL 对 RCHOP 中 2 个 R-ICE 疗程的总体缓解率约为 45%。研究者假定在复发患者的治疗方案中加入来那度胺可以使总体缓解率提高约 20％。在第 2 阶段采用中期分析的一阶段设计需要 45 位可评估的患者（单侧 α = 0.09，功效 90％）。在 I 期研究，所有类型的 B 细胞淋巴瘤均符合条件。对于 II 期研究，只有 DLBCL 患者符合中央病理学审查的标准。其他标准包括：既往接受过一线抗淋巴瘤治疗，距离上一次抗淋巴瘤治疗的结束≥2 周，HDC 和 SCT 的候选者，足够的器官（Cockcroft-肌酐清除率≥60ml / min，总胆红素≤2 ×ULN）和骨髓（ANC）≥1500/ mm^3 功储备能；血小板计数≥75,000/ mm^3）。允许在注册前 1 周使用类固醇和/或利妥昔单抗治疗。9 例患者在无 DLT 的情况下未接受 1 期临床试验，建议在研究的 2 期阶段（RP2D）中第 1 -14 天使用 20 mg 剂量。第二阶段研究通过了临时无效性分析，研究仍在继续进行。相关指标包括 Nanostring 测定来源细胞，Myc / bcl2 表达和最小残留疾病。全身 PET 扫描，包括代谢肿瘤体积。临床试验信息：NCT02628405

原文摘要：

Abstract

Background: Response rates to salvage immunochemotherapy in

patients with DLBCL relapsing after or refractory (R/R DLBCL) to front line therapy remain unsatisfactory. Lenalidomide (Len) has significant single agent activity in relapsed/refractory DLBCL. The addition of lenalidomide (Len) days 1-7 to rituximab plus ifosfamide-carboplatin-etoposide (RICE) was shown to be feasible with promising efficacy in phase 1b study (Feldman T, et al. BJH, 2014). We developed phase I/II study to evaluate the safety and efficacy of the addition of Len (extended to 14 day schedule) to RICE (R2-ICE) for R/R-DLBCL patients who are candidates for stem cell transplant.

Methods: The phase I portion was designed to determine the maximally tolerated dose Len in combination with RICE using the standard cohort 3+3 design. The escalation dose levels were 15 mg and 20 mg daily x 14 days. Prophylactic aspirin and growth factor support is mandatory. After 2 cycles of therapy response is evaluated with a PET/CT scan; the responding patients are eligible for 1-2 additional cycles of R2ICE as a bridging before HDC/SCT. The estimated overall response rate for two cycles of R-ICE in R/R DLBCL to RCHOP was estimated to be approximate 45%. We hypothesize that the addition of lenalidomide in the relapse setting could increase the overall response rate by approximately 20%. The one-stage design with an interim analysis being utilized in phase 2 requires 45 evaluable patients (one sided alpha = 0.09, power 90%). For Phase I, all types of B-cell lymphomas were eligible. For phase II portion

only DLBCL patients are eligible per central pathology review. Other eligibility criteria include: received one line of previous anti-lymphoma therapy, ⩾ 2 weeks from completion of prior anti-lymphoma therapy, candidate for HDC and SCT, adequate organ (creatinine clearance ⩾ 60ml/min by Cockcroft-, total bilirubin ⩽ 2 × ULN) and bone marrow function (ANC) ⩾1500/mm3; platelet count ⩾75,000/mm3). The use of steroids and/or rituximab up to 1 week prior to registration for management of symptoms is allowed. 9 patients cleared phase 1 without DLT and dose of 20 mg days 1 -14 was recommend for phase 2 part (RP2D) of the study. The phase 2 study passed interim futility analysis and accrual continues. Correlatives include cell of origin by Nanostring, Myc/bcl2 expression and by FISH and minimal residual disease. PET scans are centrally reviewed including metabolic tumor volume. Clinical trial information: NCT02628405

参考文献：

Guerra-Bauman F, LaPlant B, Macon WR, Witzig TE, Farooq U, Nowakowski GS and Feldman T: Phase I/II study of R-ICE (rituximab-ifosfamide-carboplatin-etoposide) with lenalidomide (R2-ICE) in patients with first-relapse/primary refractory diffuse large B-cell lymphoma (DLBCL) in academic and community cancer research united (ACCRU) network. J CLIN ONCOL 38: S8073, 2020.