Randomised phase III study of R-ICE versus R-DHAP in relapsed patients with CD20 diffuse large B-cell lymphoma (DLBCL) followed by high-dose therapy and a second randomisation to maintenance treatment with rituximab or not: an update of the CORAL study

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The multicentre phase III CORAL study aims to guide choice of salvage chemotherapy in diffuse large B-cell lymphoma (DLBCL) and assess the role of rituximab maintenance after autologous stem cell transplantation (ASCT). Patients are first randomised between ICE (ifosfamide, carboplatin, etoposide) and DHAP (dexamethasone, ara-C and cisplatin), both combined with rituximab (R-ICE or R-DHAP). After three courses, responders are treated by ASCT with BEAM. A second randomisation then allocates patients to maintenance treatment with rituximab 375 mg/m², one injection every 2 months six times, or observation. Accrual to the study is now proceeding well and the planned 400 patients are likely to be enrolled within the next 1.5 years. Results to date are very preliminary but suggest encouraging rates of response. However, they also indicate that initial exposure to rituximab may increase the difficulty of salvaging patients who fail first-line therapy.

Key words: diffuse large B-cell lymphoma, salvage treatment, rituximab, R-ICE

introduction

High-dose therapy followed by autologous stem cell transplantation (ASCT) is the treatment of choice for patients with relapsed diffuse large B-cell lymphoma (DLBCL) who are still responding to salvage therapy [1, 2]. The choice of salvage chemotherapy varies. The most frequently used regimen has been DHAP (dexamethasone, ara-C and cisplatin). However, phase II studies suggest the ICE regimen (ifosfamide, carboplatin, etoposide) induces a higher rate of remissions [3]. No randomised studies have been performed comparing these two regimens (or indeed others) in refractory/relapsed DLBCL.

Rituximab has been shown to be an important part of the first-line treatment of DLBCL [4, 5]. Rituximab is also active, both as a single agent and in combination with chemotherapy, in relapsed or resistant disease [3, 6, 7]. However, its role in the salvage therapy of patients who have already been treated with rituximab is not clear. Maintenance therapy with rituximab in patients in complete remission (CR) after ASCT is an interesting novel approach, which may eradicate minimal residual disease, but this concept has yet to be tested in a controlled study.

The principal aims of the CORAL study are to investigate the choice of salvage chemotherapy and the role of rituximab maintenance after ASCT. Tumour material is being collected in patients with relapsed DLBCL in order to learn more about lymphoma biology and optimal treatment in this situation.

patients and methods

The CORAL study is a multi-centre intergroup phase III trial in patients with relapsed/refractory DLBCL who have already received standard primary treatment. Patients with biopsy-verified partial remission on primary treatment are also eligible. Other inclusion criteria are age 18–65 years, CD20 positive disease and eligibility for transplantation.

Patients are first randomised between ICE and DHAP, both combined with rituximab (R-ICE or R-DHAP). Responders are treated by ASCT with BEAM (BCNU, etoposide, ara-C and melphalan) after three courses of R-ICE or R-DHAP. A second randomisation will then allocate patients to maintenance treatment with rituximab 375 mg/m², one injection every 2 months six times, or observation.

The primary end point in the comparison between R-ICE and R-DHAP is overall response rate (complete and partial) adjusted to successful mobilisation of stem cells (mobilisation-adjusted response rate). The primary end point of the rituximab versus observation maintenance phase is event-free survival (EFS) 2 years after ASCT. Four hundred patients will need to be randomised between the two chemotherapy arms to detect a 15% difference in mobilisation-adjusted response rate in favour of R-ICE.

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In the maintenance phase, 240 patients need to be randomised to detect a 15% difference in 2-year EFS in favour of the rituximab arm. Analysis of histological material at relapse will be performed to determine immunohistochemical characteristics and genomic profile. If possible, these data will be compared with results obtained in tissue from the initial diagnosis.

The participating groups are GELA (Groupe d’Étude des Lymphomes de l’Adulte), DSHNHL (German high-grade non-Hodgkin’s lymphoma group), NCRI (National Cancer Research Institute, UK), ALLG (Australian lymphoma study group) and SAKK (Schweizerische Arbeitsgruppe fur Klinische Krebsforschung). In addition, single centres from many different countries have joined the study. It is headed by Professor Christian Gisselbrecht, Paris, France.

results

The CORAL study started in September 2003. Eleven countries are involved, with Germany and France as the main contributors. Accrual was slow during the first months but has steadily increased and is now eight to 10 patients/month. To date, 152 of the planned 400 patients have been enrolled. Their mean age is 54 years.

Among patients included in the first randomisation, 84 (55%) had failed initial therapy and 68 (45%) had relapsed. Fifty-eight (69%) of the initially refractory patients had been exposed to rituximab while this was true of only 10 (15%) in the relapsed group. These pre-study characteristics were equally distributed between R-DHAP and R-ICE arms.

Among the first hundred patients evaluated for response, 18 patients had a PR and 43 a CR (overall response rate 61%). Of the first 100 patients randomised, 48% have proceeded to second randomisation: 30 patients had received R-DHAP salvage therapy and 28 R-ICE. Among these 58 patients, 22 (38%) had failed initial therapy following diagnosis and 36 (62%) had relapsed. No unexpected toxicities have yet been reported in the study.

discussion

The CORAL study is intended to be the largest trial in relapsed DLBCL. Given full accrual, patient numbers will exceed the former largest (PARMA) study [1]. The first phase of CORAL compares the two salvage therapies in widest use today. Besides a potential difference in remission rate (with uncontrolled studies suggesting greater efficacy with R-ICE), the two regimens differ in toxicity; R-DHAP has more renal toxicity and ICE more bone marrow toxicity. The initial phase of the study uses a novel primary end point, the mobilisation-adjusted response rate. This end point was chosen in the knowledge that long-lasting remissions are extremely rare after salvage chemotherapy alone and must be consolidated with ASCT. Thus the ability to harvest stem cells is a major goal of the regimen.

The CORAL study is especially important now that rituximab has ‘changed the lymphoma map’, so reducing the value of earlier studies. Current data from CORAL show that the majority of patients failing initial post-diagnosis therapy have been exposed to rituximab. However, this is the case in only a minority of the relapsed group.

Use of more effective rituximab-containing primary therapy in DLBCL may be making it more difficult to salvage patients who are refractory or who relapse. An indication of this phenomenon can be found in the characteristics of patients included so far in the CORAL study. Among patients who had failed initial induction, those who had been exposed to rituximab were less likely to proceed to second randomisation than those not exposed to rituximab (41% versus 69%). The low number of patients previously exposed to rituximab means that this analysis cannot yet be undertaken for relapsed patients.

The CORAL study is a unique worldwide trial investigating the important question of how best to manage patients with relapsed DLBCL. By collecting tumour material, the CORAL study also has the potential to answer important questions about lymphoma biology in the situation of relapse. At the current accelerated rate of accrual, the final patient will be enrolled within the next 1.5–2 years.

references