Non-Hodgkin lymphoma

R-GDP less toxic than R-DHAP in relapsed/refractory NHL

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TRIAL SUMMARY: GDP less toxic but equally effective relative to DHAP.

The optimum chemotherapy combination prior to autologous stem cell transplantation (ASCT) for patients with relapsed or refractory aggressive non-Hodgkin lymphomas (NHL) has not been defined. The safety and efficacy of outpatient treatment with GDP was established in a Phase II study (Crump et al, Cancer 2004) leading to this Phase III trial testing the hypothesis that GDP is as effective as and less toxic than standard DHAP, and potentially associated with better quality of life (QoL) and lower resource utilization.

Patients with relapsed/refractory aggressive NHL were stratified by IPI (International Prognostic Index) score at relapse (0, 1, 2 ≥3 risk factors), immunophenotype (B vs T cell), disease status following initial treatment (response duration <1 year vs duration >1 year vs no response/PD) and prior treatment with rituximab (R), and were randomized to 2–3 21-day cycles of G 1000 mg/m² day 1 & 8, D 40 mg day 1–4, P 75 mg/m² rituximab (R), and were randomized to 2–3 21-day cycles of duration >1 year vs no response/PD) and prior treatment with CD20+ lymphoma following initial treatment (LY12). Presented at ASH 2012. Blood 2012;120:abstr 745.

The response rate to GDP is not inferior to the standard regimen of DHAP prior to ASCT for aggressive lymphomas, and GDP resulted in similar rates of transplantation, EFS and OS. GDP can be given in the outpatient setting with significantly less toxicity, superior QoL scores and reduced need for hospitalization. This study supports the use of GDP as a new standard in practice and in future studies focused on improving salvage therapy approaches.

COMMENTARY: Treatment outcomes remain poor for the majority of patients who suffer from relapsed or refractory aggressive-histology non-Hodgkin Lymphoma (aNHL). Such patients who are not transplant-eligible because of significant comorbidities have very short survival rates, often less than 6 months. Even young healthy patients must undergo repeated cycles of a salvage chemotherapy regimen, and then proceed to myeloablative high-dose therapy (HDT) with ASCT if their disease proves chemosensitive. Over the past 2 decades, conventional salvage chemotherapy options for NHL have included regimens such as DHAP (methotrexate, cytarabine, cisplatin), ESHAP (etoposide, high-dose ara-C, cisplatin), or ICE (ifosfamide, carboplatin, etoposide). These regimens are usually administered on an inpatient basis, and are associated with substantial toxicity in terms of febrile neutropenic infection, cytopenias, alopecia, nausea and malaise. There was no
prospective randomized controlled trial (RCT) comparing these regimens until the Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL study), which compared R-DHAP to R-ICE for 396 patients with relapsed or refractory DLBCL.3 Results of the CORAL study found no significant differences between R-DHAP and R-ICE with almost two-thirds of patients responding to treatment, approximately half proceeding to ASCT and one-third achieving 3-year PFS. However, PFS was approximately 20% for patients who had initially received prior rituximab-containing induction therapy, had initial time to progression (TTP) <1 year, or had age-adjusted IPI scores=2–3.

Dr. Crump and other investigators for the NCIC CTG LY12 study need to be commended for completing the largest Phase III RCT ever performed comparing two salvage chemotherapy regimens for relapsed/refractory aNHL.4 Although the study had a long accrual period, from 2003–2011, treatment of relapsed aNHL changed little over this time except for the addition of rituximab to the salvage therapy,4,5 a modification that was incorporated into the LY12 protocol after 2005. NCIC LY12 randomized 619 patients to R-GDP or R-DHA salvage therapy. Responding patients were then to proceed to HDT/ASCT. Using a non-inferiority design, co-primary endpoints were response and transplantation rates. Because R-GDP could more easily be administered on an outpatient basis and was thought to be less toxic, important secondary endpoints of the LY12 study included toxicity and QoL. A second randomization was performed post-ASCT to either rituximab consolidation or observation for patients with CD20+ NHL, however results are not available.

The results of LY12 were reported in an oral presentation at the 2012 American Society of Hematology meeting.2 The main findings of LY12 were non-inferior response rates (45% and 44%), transplantation rates (52% and 49%), and 4-year PFS rates (25.6% and 26.1%) for R-GDP compared to R-DHAP. Also of importance, R-GDP resulted in less Grade 3-4 toxicity (47 vs 61%), less febrile neutropenia (9 vs 23%), less need for platelet transfusions (18% vs 32%) and fewer AEs requiring hospitalization (18 vs 30%), with better QoL. Although the response rates and PFS rates are numerically higher in the CORAL study, it needs to be recognized that inter-trial comparisons are unreliable because differences in treatment outcomes between trials are often due to differences in baseline patient characteristics. For example, the CORAL study only included DLBCL whereas LY12 also included T-cell NHL. In addition, only 44% of patients in the CORAL study had initial TTP <1 year compared to 73% in LY12. In opposition to the CORAL study, an important finding of the NCIC LY12 study was that patients who failed prior R-CHOP did not have worse outcomes following re-induction. This finding is supported by other reports.5,6 The authors reasonably conclude that R-GDP should be considered a new standard in practice for relapsed/refractory aNHL.

Although we may accept that R-GDP is the new standard of care for relapsed/refractory aNHL in Canada, the question is “Where do we go from here?” The main advantage of R-GDP is that it can easily be given on an outpatient basis, with similar outcomes but less toxicity than other salvage therapy options. It needs to be stated, however, that the results of all of these salvage regimens are unsatisfactory. Only 50% of patients eventually undergo HDT/ASCT and only 25–30% of patients achieve cure. Reasons for not receiving HDCT/ASCT include: chemoresistant disease; development of CNS lymphoma; organ dysfunction from comorbid illness, treatment complications or rapid disease progression; and inability to collect adequate stem cell graft secondary to marrow damage from lymphoma, chemotherapy or radiotherapy. Following R-ICE or R-DHAP in the CORAL study, 9–10% of patients failed stem cell mobilization, whereas following R-GDP or R-DHAP in the NCIC LY12 study, 12% and 18% of patients, respectively, failed to collect >2 million CD34+ cells/kg.

Similar to the many negative studies comparing frontline CHOP to other multidrug regimens, the NCIC LY12, the CORAL study, and a nonrandomized comparison of R-ESHAP to R-ICE all demonstrate that changing cytotoxic drug combinations is an ineffective strategy to improve results of salvage therapy for aNHL.1,2,8 Other strategies, therefore, must be explored, such as high-dose salvage therapy,10 use of novel agents including lenalidomide, inotuzumab ozogamicin, or bendamustine, possibly with inhibitors of DNA damage repair such as infusional gemcitabine or bortezomib plus PARP (poly [ADP-ribose] polymerase) inhibition.

Future research should also investigate whether biomarkers

**IN BRIEF**

**Already known**
- Salvage chemotherapy regimens R-ICE and R-DHAP confer similar outcomes for relapsed or refractory DLBCL patients.

**What this study showed**
- R-GDP results in non-inferior response rates, transplantation rates and PFS compared to R-DHAP, but with lower toxicity and superior QoL. R-GDP should now be considered a new standard of care for relapsed aggressive-histology NHL patients.

**Next steps**
- Improve upon R-GDP outcomes by incorporating or substituting novel, noncytotoxic or targeted agents, or comparing new or high-dose regimens to standard R-GDP in future Phase III or randomized Phase II trials.
- Use correlative science to identify and validate biomarker models that can predict benefit or futility of R-GDP salvage, and guide appropriate patients to studies investigating novel agents or approaches.
can correctly predict which patients will benefit from conventional salvage chemotherapy and HDT/ASCT, and which patients should instead be offered investigational approaches described above. For example, it is known that non-germinal centre B-cell (non-GCB) DLBCL is associated with lower PFS and OS than GCB DLBCL following initial R-CHOP induction therapy. In the BioCORAL study GCB was significantly associated with a better PFS in the R-DHAP arm.11 Interestingly, HDT/ASCT outcomes are generally not associated with GCB vs non-GCB status, suggesting that non-GCB might benefit from higher-dose salvage therapy.12 Lenalidomide has been reported to give higher response rates for relapsed non-GCB than GCB DLBCL (53% vs 9%, respectively).13 Bortezomib may also be a useful agent specifically for non-GCB relapsed DLBCL, based on the known NFkB activation in this subgroup. Also, assessment of Myc, Bcl-2, and p53 status may further prognosticate relapsed aNHL patients. In the BioCORAL study, the 17% of patients whose DLBCL contained Myc rearrangements had 4-year PFS rates of only 18% compared to 42% for other patients.14 These biomarkers should be evaluated in the LY12 patients. More recent technologies such as microRNA profiling and genome sequencing studies may one day shed more light on the best management approaches for these difficult disease situations.

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References: