Tisagenlecleucel Shows High, Durable Responses in Relapsed/Refractory Diffuse Large B-Cell Lymphoma

BACKGROUND: The prognosis is poor for patients with diffuse large B-cell lymphoma (DLBCL) whose disease relapsed or who have a resistant disease. A previous phase 2a clinical trial with the chimeric antigen receptor (CAR) T-cell therapy tisagenlecleucel showed efficacy against a variety of B-cell lymphomas. The phase 2 clinical trial JULIET investigated the use of tisagenlecleucel in adults with relapsed or refractory DLBCL.

METHODS: JULIET was a single-group, open-label, multicenter, international study of adults with relapsed or refractory DLBCL who were ineligible for, or had disease progression after, autologous hematopoietic stem-cell transplant. At the data cutoff point on March 8, 2017, among the 165 patients in the study, 111 received a single dose of tisagenlecleucel, and 92% received bridging therapy. The patients underwent restaging before an infusion, and 93% received lymphodepleting chemotherapy. The primary end point was the best overall response rate, defined as the percentage of patients who had a complete or partial response.

RESULTS: The best overall response rate was 52% among the 93 patients who had 3 months or more of follow-up, or those who had discontinued the study before 3 months, including a complete response rate of 40% and a partial response rate of 12%. The overall response rate and the complete response rate were 38% and 32%, respectively, at 3 months; at 6 months, these rates were 33% and 29%, respectively. The response rates were consistent across the prognostic subgroups. The median duration of response had not been reached at the time of analysis; however, 79% of the patients who had a complete response and 65% of all patients who had a response were projected to remain relapse-free at 12 months after responding to CAR T-cell therapy. The most common grade 3 or 4 adverse events of special interest included cytokine release syndrome (22%), neurologic events (12%), cytopenia lasting more than 28 days (32%), infections (20%), and febrile neutropenia (14%). No deaths, cytokine release syndrome, or cerebral edema were reported with tisagenlecleucel treatment.

Patients with relapsed or refractory DLBCL who are not eligible for high-dose therapy and hematopoietic-cell transplantation or for whom such therapy was not successful have very few treatment options,” the researchers noted. “For these patients, tisagenlecleucel shows promise that will need to be confirmed through larger studies with longer follow-up.”

Olaparib Maintenance Extends Progression-Free Survival in Advanced Ovarian Cancer

BACKGROUND: Currently, limited therapies are available to prevent or delay recurrence in advanced ovarian cancer, with approximately 70% of patients having a disease recurrence within 3 years of treatment. The effectiveness of olaparib, an oral poly(ADP-ribose) polymerase (PARP) inhibitor, in relapsed disease has been well-established; however, its benefit as a maintenance therapy in newly diagnosed advanced ovarian cancer is uncertain. In a recent study, researchers evaluated the efficacy of upfront maintenance therapy with this PARP inhibitor in patients with newly diagnosed, advanced BRCA-positive ovarian cancer.

METHODS: The SOLO1 study was a randomized, double-blind, placebo-controlled, phase 3 clinical trial that enrolled 391 patients with newly diagnosed, histologically confirmed, advanced high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer, or fallopian tube cancer and germline or somatic BRCA mutations. All patients had cytoreductive surgery, received platinum-based chemotherapy, and had a complete or a partial response to therapy. The patients were randomized in a 2:1 ratio to olaparib tablets 300 mg twice daily or to placebo, for 2 years. The primary endpoint was progression-free survival (PFS), as assessed by the investigators.

RESULTS: After a median follow-up of 41 months, the risk for disease progression or death at 3 years was 70% lower with olaparib than with placebo (95% confidence interval, 0.20-0.41; P <.001). The placebo arm had a median PFS of 13.8 months, whereas the median had yet to be reached in the olaparib arm. Furthermore, in the olaparib arm, improvement in PFS was maintained after stopping treatment at 2 years.

Olaparib was well-tolerated and its safety profile was consistent with what was observed in the relapsed disease setting. The most common grade 3 or 4 adverse events in patients who received olaparib were anemia (22%) and neutropenia (9%). The rates of adverse events that led to a dose reduction or study drug discontinuation were relatively low; only 12% of the patients discontinued olaparib because of adverse events.

“In conclusion, the SOLO1 trial showed that the use of maintenance therapy with olaparib, as compared with placebo, after platinum-based chemotherapy provided a substantial benefit with regard to progression-free survival among women with newly diagnosed advanced ovarian cancer and a BRCA1/2 mutation,” the researchers observed.


Ibrutinib Superior to Standard Chemoimmunotherapy in Older Patients with Chronic Lymphocytic Leukemia

BACKGROUND: Chemoimmunotherapy with chlorambucil plus obinutuzumab or with bendamustine plus rituximab is a standard first-line treatment for older patients with chronic lymphocytic leukemia (CLL). However, chemoimmunotherapy is associated with significant toxic effects, and the risk for adverse effects increases with age. For patients with CLL, first-line ibrutinib monotherapy is widely used in clinical practice. The benefit of this Bruton’s tyrosine kinase (BTK) inhibitor versus chemoimmunotherapy remains a critical consideration, which led researchers to conduct a head-to-head phase 3 clinical trial to evaluate the efficacy of ibrutinib, alone or in combination with rituximab, relative to chemoimmunotherapy.

METHODS: The Alliance North American Intergroup Study A041202 included treatment-naïve, intermediate- or high-risk patients aged 65 years who were diagnosed with CLL. A total of 547 patients were randomized in a 1:1:1 ratio to ibrutinib monotherapy,
ibrutinib plus rituximab, or bendamustine plus rituximab. Bendamustine 90 mg/m² was given on days 1 and 2 of each 28-day cycle plus rituximab 375 mg/m² on day 0 of cycle 1, then rituximab 500 mg/m² on day 1 of cycles 2 to 6. Oral ibrutinib was given at 420 mg daily. In the ibrutinib combination arm, rituximab was given at 375 mg/m² weekly for 4 weeks starting on day 1 of cycle 2, and then on day 1 of cycles 3 to 6. Patients received treatment until disease progression or unacceptable toxicity. Patients in the bendamustine group whose disease progressed were allowed to cross over to the ibrutinib monotherapy arm. The primary end point was progression-free survival (PFS), and the secondary end point was overall survival.

**RESULTS:** The addition of rituximab to ibrutinib had no additional PFS benefit. At 2 years, the PFS rates were 74% with bendamustine plus rituximab versus 87% with single-agent ibrutinib and 88% with ibrutinib plus rituximab. No significant differences in PFS were observed between the ibrutinib plus rituximab group and the ibrutinib monotherapy group (P = .49).

“Improvement in overall survival is the ultimate goal of new therapies, and in this analysis, there was no significant difference among the 3 treatment groups with regard to overall survival, although the follow-up period was short for this disease,” the researchers noted.

The rate of grade 3 or 4 hematologic events was higher in the bendamustine arm (61%) than in the ibrutinib arm (41%) or the ibrutinib plus rituximab arm (39%). However, grade 3 or 4 nonhematologic adverse events were more common in the 2 ibrutinib arms (74% in each) than in the bendamustine arm (63%).

“The results of this analysis show the efficacy of treatment with continuous ibrutinib among patients with untreated CLL, but the results also raise the issue of whether indefinite therapy with a BTK inhibitor is needed,” the authors suggested. They noted that 2 upcoming studies in this patient population may help address this issue.


**COMMENTARY BY ROBERT J. IGNOFFO**

The results from this randomized clinical trial of oral ibrutinib versus combination chemoimmunotherapy are impressive in terms of PFS at 2 years. The ibrutinib group clearly has a greater proportion of patients free of progression. However, because overall survival was not different among the 3 groups, the question of long-term benefit with this therapy remains open.

For each of the subgroup analyses, the ibrutinib groups had a significantly smaller hazard ratio than the non-ibrutinib groups. Furthermore, because no significant difference was seen in PFS between the ibrutinib-alone versus ibrutinib plus rituximab arms, this favors the use of the single agent. In the subgroup analysis, cytogenetics appeared to play a role in PFS, which was longer in ibrutinib-containing regimens compared with bendamustine plus rituximab for patients with deletion in chromosome 17. The overall response rate was greater in the ibrutinib group (93%) compared with the bendamustine group (87%), but the rate of complete responses was greater (26%) in the bendamustine plus rituximab arm versus 6% and 12% for the 2 ibrutinib-containing regimens.

Further study is needed to determine how long to use ibrutinib therapy in older patients, but it appears that this drug, alone or in combination with rituximab, is superior to bendamustine plus rituximab in terms of PFS. At the time of data cutoff, the duration of ibrutinib therapy was 32 months. Until further data become available, it is reasonable to continue the use of ibrutinib therapy, alone or in combination with rituximab, until disease progression.