Anti-CD19 CAR T-Cells Show Promise in B-Cell Cancer

BACKGROUND: Patients with chemotherapy-refractory diffuse large B-cell lymphoma (DLBCL) have limited treatment options and a median survival of <10 months. Although recent advances have improved the treatment of B-cell malignancies, new treatments for chemotherapy-refractory cases are needed. Previous reports showed that a single infusion of autologous T-cells that express anti-CD19 chimeric antigen receptor (CAR) in patients with indolent B-cell malignancies led to lengthy remissions. In what is believed to be the first study of its kind, researchers evaluated the safety and efficacy of autologous anti-CD19 CAR T-cells in patients with advanced CD19-positive B-cell malignancies.

METHODS: The study included 15 patients with advanced B-cell malignancies. Of these, 9 patients had DLBCL, with 3 different subtypes: 4 patients had primary mediastinal B-cell lymphoma, 4 patients had DLBCL not otherwise specified, and 1 patient had DLBCL transformed from chronic lymphocytic leukemia (CLL). In addition, 2 patients had indolent lymphomas, and 4 had CLL.

All patients received an initial conditioning chemotherapy regimen consisting of cyclophosphamide at a total dose of 120 mg/kg to 60 mg/kg followed by 5 daily infusions of fludarabine 25 mg/m². A day later, patients received a single infusion of anti-CD19 CAR T-cells.

RESULTS: Of the 15 patients, 8 achieved complete remission, 4 achieved partial remission, 1 had stable disease, and 2 were not evaluable for response. In the subgroup of 9 patients with DLBCL, 4 of 7 evaluable patients with chemotherapy-refractory DLBCL had complete remission; 3 of these 4 patients are in ongoing complete remission, with durations ranging from 9 to 22 months.

Of the patients with DLBCL, 2 achieved partial response, and 1 achieved stable disease. In the subgroup of 6 patients with indolent B-cell malignancies, all patients achieved a complete remission or partial remission; 3 of 4 patients with CLL are in ongoing complete remission ranging from 14 to 23 months.

The peak level of CAR-positive blood cells varied among patients from 9 to 777 CAR-positive cells/µL. These levels peaked between 7 and 17 days after infusion. Grade 3 and 4 acute toxicities included fever, hypotension, delirium, and other neurologic toxicities; these toxicities were transient and resolved within 3 weeks after cell infusion.

This is the first study to show a successful treatment of DLBCL with anti-CD19 CAR T-cells. The majority of patients with chemotherapy-refractory DLBCL and indolent B-cell malignancies achieved complete remission; these findings demonstrate the feasibility and effectiveness of treating this patient population with anti-CD19 CAR T-cells.

Infusion with anti-CD19 CAR T-cells may offer a powerful new treatment option for patients with chemotherapy-refractory B-cell malignancies. The researchers recommended further development of this approach for advanced B-cell malignancies.

Lenvatinib Prolongs Progression-Free Survival in Advanced Thyroid Cancer

BACKGROUND: Lenvatinib (Lenvima) is a novel oral multitargeted tyrosine kinase inhibitor (TKI) that inhibits vascular endothelial growth factor receptors 1, 2, and 3; fibroblast growth factor receptors 1 to 4; platelet-derived growth factor receptor alpha; RET; and KIT-signaling networks. In a phase 2 study of patients with radioactive iodine therapy–refractory differentiated thyroid cancer, lenvatinib demonstrated clinical benefit. Based on these results, researchers conducted a phase 3 study to assess progression-free survival (PFS) among patients who received lenvatinib compared with placebo.

METHODS: The SELECT study was a randomized, double-blind, placebo-controlled, multicenter, phase 3 study involving 392 patients with progressive differentiated thyroid cancer that was refractory to radioactive iodine therapy. Patients were randomized in a 2:1 ratio to lenvatinib 24 mg daily in 28-day cycles (N = 262) or to placebo (N = 131). Pretreatment with 1 previous TKI regimen was permitted. At disease progression, patients in the placebo group could receive open-label lenvatinib. The median duration of treatment was 13.8 months for the lenvatinib group and 3.9 months for the placebo group. The primary end point was PFS, and the secondary end points were response rate, overall survival, and safety.

RESULTS: The median PFS was 18.3 months among the patients who received lenvatinib compared with 3.6 months with placebo, a 14.7-month PFS extension with active treatment (hazard ratio for disease progression or death, 0.21; 99% confidence interval, 0.14-0.31; P < .001). This is the longest improvement in PFS observed in studies comparing active drug therapy and placebo in patients with differentiated thyroid cancer.

The PFS benefit associated with lenvatinib was observed in all prespecified groups. Lenvatinib was associated also with a significantly greater patient response rate compared with placebo—64.8% versus 1.5%, respectively. Furthermore, more complete and partial responses were observed with lenvatinib than with placebo (4 and 165 vs 0 and 2, respectively). The median overall survival was not reached in either group.

Adverse events of any grade, which occurred in >40% of patients in the lenvatinib group, included hypertension (67.8%), diarrhea (59.4%), fatigue or asthenia (59.0%), decreased appetite (50.2%), decreased weight (46.4%), and nausea (41.0%). The most frequently reported grade ≥3 adverse events reported in the lenvatinib group included hypertension (41.8%), proteinuria (10.0%), decreased weight (9.6%), fatigue (9.2%), and diarrhea (8.0%).

A total of 37 patients in the lenvatinib group and 3 patients in the placebo group discontinued treatment because of adverse events.

The 10-year survival rate for patients with differentiated thyroid cancer refractory to radioactive iodine therapy is 10% from time of metastasis. Lenvatinib was associated with significant improvement in PFS and response rate among patients with progressive, radioactive iodine–refractory, differentiated thyroid cancer, which offers a new treatment option for this patient population. Although the toxic effects of lenvatinib therapy were considerable, most toxic effects were managed with dose modification and medical therapy. Based on these results, in February 2015, the US Food and Drug Administration approved lenvatinib for the treatment of patients with differentiated thyroid cancer that is refractory to radioactive iodine therapy.


COMMENTARY BY ROBERT J. IGNOFFO

This study, which was funded by Eisai Inc, demonstrated that lenvatinib greatly improves progression-free survival (PFS) in patients with refractory thyroid cancer. Compared with placebo, lenvatinib produced a nearly 15-month improvement in PFS. Grade 3 or 4 toxicities were typical for a multitargeted tyrosine kinase inhibitor, with hypertension, fatigue, diarrhea, and proteinuria being the predominant adverse effects. Hand-foot syndrome, nausea, vomiting, stomatitis, and decreased appetite were also common.

These results are better than those reported in the DECISION trial (also funded by pharma), which compared the safety and efficacy of sorafenib with placebo in patients with radioiodine-refractory thyroid cancer.

Until lenvatinib receives US Food and Drug Administration approval, sorafenib will remain one of the most effective treatments for patients with differentiated thyroid cancer that is refractory to radioiodine.

Ruxolitinib More Effective Than Standard Therapy in the Treatment of Polycythemia Vera

BACKGROUND: Polycythemia vera, a myeloproliferative neoplasm characterized by elevated red blood cell levels, poses an increased risk for thrombotic and cardiovascular events and a significant clinical burden. If untreated, polycythemia vera can transform to myelofibrosis or to acute myeloid leukemia. Based on earlier results of a phase 2 study, researchers conducted a new phase 3 clinical study to evaluate the clinical benefit of ruxolitinib (Jakafi), a Janus kinase (JAK) 1 and 2 inhibitor, versus standard therapy in patients with polycythemia vera that was resistant to standard therapy with hydroxyurea. Standard therapy was selected by the investigator and could include hydroxyurea, interferon alfa or pegylated interferon, pipobroman, anagrelide, immunomodulators such as lenalidomide or thalidomide, or no medication. The study was funded by Novartis and Incyte companies.

METHODS: The study included 222 patients with polycythemia vera requiring phlebotomy control, with a spleen volume of ≥450 cm³, and no previous treatment with a JAK inhibitor participating in the RESPONSE trial. The RESPONSE study was an international, randomized, open-label, multicenter, phase 3 clinical trial that randomized phlebotomy-dependent patients with splenomegaly in a 1:1 ratio to a 10-mg twice-daily dose of ruxolitinib (N = 110) or to standard therapy (N = 112) selected by the investigator.

The primary end point was hematocrit control through week 32 and at least a 35% reduction in spleen volume at week 32. The Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) was used to evaluate symptom outcomes.

RESULTS: The median exposure time to therapy was 81 weeks in the ruxolitinib group and 34 weeks in the standard therapy group. Significantly more patients receiving ruxolitinib achieved the primary end point compared with the standard therapy group (20.9% vs 0.9%, respectively). Furthermore, ruxolitinib was associated with a higher rate (60%) of hematocrit control through week 32 compared with standard therapy (19.6%) (including hydroxyurea in 58.9% of the patients, interferon in 11.6%, anagrelide in 7.1%, immunomodulators in 4.5%, and pipobroman in 1.8%; no medication was administered in 15.2%). In addition, 38.2% and 0.9% of patients in the 2 groups, respectively, had at least a 35% reduction in spleen volume. Ruxolitinib was also associated with a significantly higher rate of complete hematologic response compared with standard therapy (23.6% vs 8.9%, respectively).

Overall, 49% of patients in the ruxolitinib group had at least a 50% reduction in the MPN-SAF total symptom score at week 32 versus 9% in the standard therapy group. The ruxolitinib group also maintained their primary response at week 32 through week 48 compared with the standard therapy group (19.1% vs 0.9%, respectively).

Because crossover was allowed, the impact of ruxolitinib on overall survival could not be determined.

In terms of safety, ruxolitinib was associated with a greater incidence of grade 3 or 4 anemia and thrombocytopenia (2% and 5%, respectively) compared with standard therapy (0% and 4%, respectively). Grade 1 and 2 herpes zoster infection occurred in 6% of patients receiving ruxolitinib versus no patients in the standard therapy group. Grade 3 and 4 toxicities were less with ruxolitinib compared with the standard therapy group. Fewer patients discontinued ruxolitinib therapy compared with standard therapy.

However, through week 32, more patients (N = 6) in the standard therapy group had thromboembolic events compared with the ruxolitinib group (N = 1).

The US Food and Drug Administration approved ruxolitinib for the treatment of patients with polycythemia vera in December 2014.


COMMENTARY BY ROBERT J. IGNOFFO

In addition to the increased risk of clotting, constitutional symptoms associated with polycythemia vera (eg, itching, sweating, and fatigue) are particularly bothersome. This randomized trial showed that ruxolitinib is well-tolerated and significantly more effective than standard therapies in controlling hematocrit levels, reducing spleen volume, and improving polycythemia vera–related symptoms in patients who have had inadequate responses to, or unacceptable side effects from, hydroxyurea.

Although survival benefits could not be demonstrated for ruxolitinib because of the study design, the benefits of effective hematocrit control and improved quality of life were significant.

Ruxolitinib is an important new drug in the treatment of refractory polycythemia vera, especially in patients with spleen-related symptoms who have progressed or experienced severe adverse effects from hydroxyurea.