Randomized Placebo-Controlled Double-Blind Phase II Study of Zaltoprofen for Patients with Diffuse-Type and Unresectable Localized Tenosynovial Giant Cell Tumors: The REALIZE Study

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INTRODUCTION: A tenosynovial giant cell tumor (TGCT) is a locally aggressive benign neoplasm arising from intra- or extra-articular tissue, categorized as localized (L-TGCT, solitary lesion) and diffuse (D-TGCT, multiple lesions) TGCT. Surgical excision is the mainstay of the treatment, and a high local recurrence rate of approximately 50% has been reported. We focused on zaltoprofen, a nonsteroidal anti-inflammatory drug that can activate peroxisome proliferator-activated receptor gamma (PPARγ) and inhibit the proliferation of TGCT stromal cells. Therefore, we conducted a randomized trial to evaluate the safety and effectiveness of zaltoprofen in patients with D-TGCTs or unresectable L-TGCTs.

METHODS: This randomized, placebo-controlled, double-blind, multicenter trial evaluated the safety and efficacy of zaltoprofen. In the treatment group, zaltoprofen (480 mg/day) was administered for 48 weeks; the placebo group received similar dosages without zaltoprofen. The primary outcome was progression-free rate (PFR) 48 weeks after treatment administration. Disease progression was defined as the following conditions requiring surgical intervention: 1) repetitive joint swelling due to hemorrhage; 2) joint range of motion limitation, 3) invasion of the adjacent cartilage or bone, 4) severe joint space narrowing, and 5) increased tumor size (target lesion).

RESULTS: Forty-one patients were allocated to the zaltoprofen (n=21) or placebo (n=20) groups (Table 1). The PFR was not significant between the zaltoprofen group (group Z) and the placebo group (group P) at 48 weeks (84.0% and 90.0%, respectively; p=0.619) (Fig. 1). Based on the RECIST criteria, PFRs determined by the local investigator were 95% and 94.1% in group Z and 100% and 100% in group P at 24 and 48 weeks, respectively, whereas those judged by the central committee radiologist were 95% and 100% in group Z and 94.7% and 83.3% in group P at 24 and 48 weeks, respectively. No significant differences were observed between groups Z and P (Table 2, Fig 2). The mean Musculoskeletal Tumor Society score significantly improved from baseline to week 48 in the zaltoprofen group (83.8% versus 93.0%, p=0.02), whereas that in the placebo group did not significantly improve (82.2% and 86.8%, respectively; p=0.167) (Fig. 3). One severe adverse event (grade 3 hypertension) was observed in the zaltoprofen group.

DISCUSSION AND CONCLUSION:

This is the first study to evaluate the efficacy and safety of zaltoprofen in patients with TGCT. No significant differences in PFR were observed between the groups at 48 weeks. Physical function significantly improved after zaltoprofen treatment. The safety profile of zaltoprofen was acceptable. This less invasive and safer treatment with zaltoprofen, compared to surgical removal, could be justified as a novel approach to treating TGCT. Further analysis of long-term administration of zaltoprofen should be considered in future studies.

Fig.1: Progression-free rate based on the original criteria assessed by the local investigator (a) and central committee radiologist (b). The progression-free survival rates were 84.0% in group Z and 90.0% in group P at 48 weeks (p=0.619) (a) and 84.0% in group Z and 90.0% in group P (p=0.609) (b). Group z, zaltoprofen group; group P, placebo group.

Fig.2: Response of the target tumor size on MRI in patient ZLT-01-08 (a). The reduction rates were 15.4% at 24 weeks and 10% at 48 weeks, as judged by the local investigator, and 31.4% at 24 weeks and 30.5% at 48 weeks, as judged by the central committee radiologist. Metabolic response of the target tumor size on FDG-PET in patient ZLT-01-08 (b). Reduction rates were 59.2% at 24 weeks and 70.4% at 48 weeks.

Fig.3: The mean Musculoskeletal Tumor Society (MSTS) scores were 83.81% in group Z (n=21) and 82.17% in group P (n=20) at baseline. The mean MSTS scores in group Z were 88.57% at 24 weeks and 92.96% at 48 weeks. There was a significant difference between the values at baseline and 48 weeks (p=0.020). The mean MSTS scores in group P were 86.84% at 24 weeks and 86.49% at 48 weeks. There was no significant difference between the values at baseline and 48 weeks (p=0.208).