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Prognosis value of S45F mutation of CTNNB1 in desmoid-type fibromatosis (DF). Prospective analysis of 500 consecutive patients (pts) from ALTITUDES Trial.

Introduction

DF rare locally aggressive fibroblastic non-metastasizing tumor, with an unpredictable course. Its management is challenging, there is a current shift in standard of care from large surgical resection (SR) to active surveillance (AS). Most of DF display somatic mutation of CTNNB1, with three major hotpots: S45F, T41A and S45P. The poor prognosis of S45F is a matter of debate (Timbergen et al. Ann Surg 2019). We present herein the results of the 1st Work package of ALTITUDES aiming to prospectively assess the prognostic value of CTNNB1 mutational status.

Method.

ALTITUDES (NCT02867033) is a nationwide prospective registry of DF, diagnosed from January 2016 to December 2020 and confirmed by central pathological review. CTNNB1 mutations were identified by NGS. ALTITUDES include 8 Work packages. Primary endpoint of 1st Work package was event-free survival (including disease progression or relapse). We have selected pts managed by AS, SR or systemic treatments as front-line. Prognostic factors were assessed using univariate and multivariate Cox Model.

Results

From the 630-pts enrolled in ALTITUDES, 500 (79.3%) were eligible for the present work package. Exclusion criteria were diagnosis before 2016 in 13 pts, multiple DF in 33 pts, 39 pts without CTNNB1 mutation analysis, and 45 pts receiving other treatments. The study population included 349 females (69.8%); the median age was 40 years (range 1-89). Abdominal wall was the most common primary site: 161 pts (32.2%). In 430 (86.0%) cases, there was a CTNNB1 mutation, including, S45F in 56 cases (11.2%). In 70 cases (14.0%), we did not identify CTNNB1 mutation. The front-line managements were AS in 361 pts (72.2%), SR with R0/R1 margins in 57 cases (11.4%) and systemic treatments in 82 pts (16.5%). The median follow-up was 23 months (Range, 0.4-55). Overall, progression or relapse occurred in 128 pts (25.6%). We observed a significant EFS-difference between treatment groups, both in univariate and multivariate analysis with, compared to AS, a better outcome in patients with SR and worse outcome in patients who had received a systemic treatment (p=0.01 in multivariate analysis). The risk of event was significantly associated with the tumor size, with a HR=1.46 in tumors larger than 50 mm compared to smaller tumors (95%CI, 1.01-2.10, p=0.04). We did not observe any significant association between the CTNNB1 mutational status and the outcome: compared to patients with another mutation, the hazard ratio associated with a S45F mutation was HR=0.84 (95%CI, 0.48-1.46, p=0.53) in multivariate analysis. Age, gender and location (abdominal wall *versus* other) were not associated with EFS.

Conclusion

In this large prospective study, S45F was not an independent poor prognostic factor in DF. Size and front-line treatment drive the outcome. The understanding and prediction of natural course of DF require further studies. In 2021, the 2 next ALTITUDES work packages will focus on the role of oral contraception and pregnancies on DF course (WP2) and incidence and

impact of pain on Health-related quality of life in DF patients. From 2022, the other WPs (3 to 8) will aim to better understand the mechanisms of DF progression (role of immune cells in stroma, proteomic, radiomic …).