主論文の要旨

Muscle wasting associated with the long-term use of mTOR inhibitors

（mTOR 阻害薬の長期投与に伴う筋肉量低下に関する検討）

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Introduction

Loss of muscle mass is termed sarcopenia. Sarcopenia is an important concept in oncology because low muscle mass is now known to be associated with poor prognoses and treatment toxicities in a variety of cancers. Sarcopenia also forms an important component in the definition of cancer cachexia. However, the role of various cancer drugs on muscle mass has not been properly elucidated.

The PI3K/AKT/mTOR pathway plays a key role in muscle metabolism. In vivo experiments in mice suggest that upregulating this pathway leads to muscle hypertrophy while inhibiting this pathway blocks hypertrophy. A multikinase inhibitor, sorafenib, is known to decrease muscle mass in cancer patients presumably due to the blockade of this pathway. However, the impact of long-term use of mTOR inhibitors (everolimus and temsirolimus) on muscle mass is not known yet.

Methods

This was a retrospective study conducted in Nagoya University Hospital and the Japanese Red Cross Nagoya Daiichi Hospital. The primary objective was to evaluate the change in muscle mass in cancer patients who had taken an mTOR inhibitor (everolimus or temsirolimus) as a single drug for at least 6 months. Body composition parameters (including muscle mass) were computed at baseline and after the use of the drug from CT scans of abdomen at L3 level using a software Sliceomatic 5.0 (TomoVision, Inc., Magog, QC, Canada) that provides the areas in cm^2. These areas were then divided by the square of body height to get indices such as skeletal muscle index (SMI). Lean body mass (LBM) was calculated using the formula: LBM (kg) = 0.30 x (skeletal muscle area at L3 CT scan in cm^2) + 6.06. The differences in various parameters between baseline and after treatment were examined for significance with paired t-test and performed using SPSS software, version 22.0 (IBM SPSS, Armonk, NY, USA).

Results

Among a total of 75 patients who had received mTOR inhibitor therapy during the specified period, 20 met the inclusion criteria and were included in the present study (Fig. 1). The mean duration of mTOR inhibitor use was 14.1±2.1 months, and the mean duration between the first and final CT scans was 14.4±2.0 months. All patients had metastatic renal cell carcinoma, with the exception of two who had metastatic pancreatic neuroendocrine tumors (Table I).

A total of 16 patients (80%) suffered a loss of the SMT area, SMI and LBM following at least 6 months of drug use compared with the baseline. The number of

sarcopenic patients increased post-therapy (75%) compared with the baseline (60%; Table I). There was no significant change in body weight or adipose tissue mass. However, skeletal muscle area, SMI and LBM all decreased significantly following treatment (Table II). The rate of muscle loss was by 2.6 cm^2/m^2 or 2.3kgs in 6 months. We also found that the lower the baseline SMI, the less the decrease in muscle mass. Finally, taking the median SMI as the cut-off value based on gender, the median TTF was longer in the non-sarcopenic arm (15.7 months) compared with the sarcopenic arm (12.9 months), although the difference was not significant (P=0.819; Fig. 2).

Discussion

To the best of our knowledge, this is the first study to demonstrate that the long-term use of mTOR inhibitors significantly decreases the muscle quantity, without affecting body weight and adipose tissue. The present study has also shown that the amount of the decrease in muscle mass was associated with the baseline muscle mass. TTF was not associated with the sarcopenia status of the patients.

Because cancer cachexia itself leads to muscle loss, it is difficult to distinguish between drug-induced sarcopenia and disease-induced sarcopenia in cancer patients. Thus, we included only those patients with at least 6 months of drug therapy to rule out disease-induced sarcopenia because cancer cachexia usually progresses fast and is accompanied by loss of body weight. There was no loss of body weight in our study. Seven patients in our study suffered muscle loss despite gaining body weight. Hence, body weight cannot and should not replace muscle mass measurement. Also, increase in body weight may not always be reassuring because a patient can continue to lose muscle despite gains in body weight.

One interesting finding in the present study was that patients who had a low muscle mass at the baseline suffered less muscle loss during treatment compared with patients who had greater muscle mass at the baseline. Given the important role of the mTOR pathway in muscle synthesis, patients who have low muscle mass at the baseline may also have low levels of mTORC1 receptors at the baseline, compared with patients with comparatively more muscle mass. Thus, the effect of mTOR inhibition may not be as pronounced in patients with low muscle mass at the baseline.

Unlike other studies, the present study was not able to demonstrate significantly shorter TTF of sarcopenic patients compared with those without sarcopenia. This could be due to the exclusion of patients with rapid disease progression in our study, as only those patients with at least 6 months of continuous therapy with

mTOR inhibitors were included. Alternatively, for patients who received mTOR inhibitor therapy for more than 6 months, sarcopenia may not be a poor prognostic factor, unlike the situation with other drugs.

Conclusions

In conclusion, the present study has revealed the sarcopenic effect of long-term mTOR inhibitor use, and the importance of making an assessment of muscle mass independently of body weight or the measurement of BMI. Due to the predictive and prognostic role of sarcopenia in cancer patients, this finding may have important therapeutic implications