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EDITORIAL

More than 6 months of postoperative adjuvant chemotherapy results in loss of skeletal muscle: a challenge to the current standard of care

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In Japan, patients with curatively resected stage II/III gastric cancer undergo postoperative adjuvant chemotherapy with single agent S-1 for 12 months as a standard of care. This treatment is not comfortable for everyone, however, and only 340 of 517 patients (65.8 %) who were randomized to receive the S-1 monotherapy were able to complete the 12-month treatment in the phase III trial that eventually generated the hard evidence for this strategy [1]. Compliance to the treatment is expected to be even lower among the general population outside the trial, which likely includes a higher proportion of elderly patients and those with comorbidities that render patients vulnerable to adverse events. A physician is therefore encouraged to modify the dose or the schedule appropriately with the goal of assisting each patient to adhere to the evidence-based treatment.

More recently, investigators in Yokohama identified body weight loss following surgery as a significant independent risk factor for treatment discontinuation [2]. The 6-month continuation rate was 66.4 % among patients with body weight loss less than 15 % whereas it declined to 36.4 % among those with loss of 15 % or more. These findings prompted physicians to consider early postoperative enteral nutrition to minimize the inevitable weight loss following gastrectomy, and several trials to prove the benefit of such approach are currently ongoing. In the meantime, another active group of investigators in Osaka reported in a recent article published in Gastric Cancer that a group of patients who tolerated adjuvant S-1 monotherapy for 6 months or more after receiving total gastrectomy carry a significant risk for greater than 10 % loss of skeletal muscle when compared with those who failed to do so [3]. In contrast, the duration of chemotherapy did not affect the degree of loss in total body weight or fat mass. When the findings in Yokohama and Osaka are combined, one would reach the conclusion that the patients who did not suffer from overt weight loss after total gastrectomy are more likely to receive adjuvant chemotherapy as planned but are also at risk of losing substantial lean body mass. This expectation would seem rather odd because the patients who continued with S-1 monotherapy beyond 6 months should have been in more favorable health status to be able to do so. In other words, mechanisms behind the loss of skeletal muscle among patients who were actually fit enough to tolerate chemotherapy as scheduled remain ambiguous.

Theoretically, four factors could be involved in the loss of skeletal muscle: impaired food intake, malabsorption of the relevant nutrients, lack of physical activity, and rhabdomyolysis. Of these, the decrease in oral food intake, inevitable after total gastrectomy, cannot fully explain the selective loss of skeletal muscle among the group of patients who tolerated 6 months or more of S-1 whereas the degree of loss in body weight and fat mass had been equivalent in both groups. On the other hand, treatment associated with fatigue could render patients inactive, and the lack of physical activity as a consequence could lead to the loss in skeletal muscle. Several investigators have actually highlighted a trend for lean body mass loss although fat mass is significantly increased during chemotherapy for breast cancer [4]. Patients who tolerated the treatment for 6 months or more should generally have been

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in better physical status, however, and selective loss of skeletal muscle despite this would still require explanation. As for the issue of malabsorption, prolonged administration of S-1 could cause mucosal damage, which could have selectively hindered absorption of key nutrients such as amino acids that will eventually constitute skeletal muscle. Administration of nutrients such as glutamine that nourish and preserve the mucosa might then have a supportive role in preventing the loss of lean body mass. Unfortunately, it is unknown whether the patients who suffered from loss of lean body mass in the Osaka study actually suffered from diarrhea or had any other signs suggestive of malabsorption. Finally, although rhabdomyolysis has been reported in conjunction with S-1, its incidence is considered to be extremely low. To account for the paradoxical phenomenon they have observed, the authors in Osaka proposed the role of oxidative stress, which is known to be mediated by anthracyclines, particularly doxorubicin, to induce weakness and fatigue in striated muscle [5]. It is unknown whether the same mechanism applies to S-1, a fluoropyrimidine. To summarize, the reason that the evidence-based continuation of S-1 leads to loss of skeletal muscle remains at best speculative.

What would the eventual oncological consequences be? The loss in muscle mass actually had no impact on survival in the Osaka study [3]. However, patients who received S-1 monotherapy for more than 6 months should have benefited from adherence to the treatment, given that the standard of care is to deliver S-1 for 12 months. The treatment for those who quit short of 6 months could theoretically have been suboptimal. We might have to assume, then, that the loss of skeletal muscle or any metabolic changes related to that clinical manifestation actually had a negative impact on survival so as to nullify the benefit of being fit enough to fully receive the planned chemotherapy. This idea could be the most pessimistic assumption, which we hope is proved wrong, and is, admittedly, a skewed interpretation, disregarding the influence of various biases inherent to a retrospective study. Also, we currently have few data to prove that 12 months of postoperative treatment is superior to 6 months (S-1 for 12 months was superior to surgery alone) [1].

In 2011, we proposed a hypothesis that laparoscopic surgery could avoid the loss of lean body mass through offering patients opportunities for earlier return to physical activities [6]. However, it would now seem that the combined effect of minimally invasive surgery, gastrectomy, nutritional status, and postoperative chemotherapy on body composition is much more complex to analyze than we had imagined at that time. There is a currently strong trend in Japan of patients who are diagnosed to have gastric cancer becoming older, frailer, and lonelier with few family members to support their lives postoperatively. Further knowledge is mandatory in this field of research to grasp how we can appropriately assist our patients to recover from the detrimental effect of gastric surgery while enduring postoperative adjuvant therapy to cure cancer.

Will surgery by laparoscopic approach be of any help? Should the patients be exposed to physical exercise postoperatively [7]? Or should the postoperative chemotherapy be shortened to 6 months? Nobody should jump to a conclusion, but the provocative hypothesis raised in Osaka might be one of some aspects to remember when considering postoperative chemotherapy for gastric cancer.

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