

## Can the ARTISTs complete the Schubert Unfinished (Sinfonie Nr. 7 in h moll D. 759 "Die Unvollendete")?

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*Transl Gastrointest Cancer* 2012;1:117-118. DOI: 10.3978/j.issn.2224-4778.2012.02.02

Surgery, chemotherapy, and radiotherapy are proven treatment options for gastric cancer. D2 lymph node dissection has become a standard surgical technique after its usefulness was demonstrated by Sasako and colleagues as well as based on the findings of a 15-year follow-up in the Dutch Gastric Cancer Group assessed by Songun and colleagues (1,2).

Compared with D2 dissection alone, the survival time was prolonged in the S-1 monotherapy arm in the ACTS-GC study by Sakuramoto and colleagues and in the XELOX therapy arm in the CLASSIC study by Bang and colleagues. Both studies reported the usefulness of adjuvant chemotherapy even in patients treated with D2 dissection. The subgroup analysis in the ACTS-GC study showed the surgery/adjuvant chemotherapy combination was useful for the treatment of stage II to IIIA gastric cancer treated with S-1 alone but not for cancer of stage IIIB or higher. On the other hand, the CLASSIC study showed the usefulness of XELOX therapy in all cancer stages (II to IIIB), suggesting the combination therapy will be required for the treatment of stage IIIA or higher gastric cancer (3,4).

The Intergroup 0116 study reported a prolonged survival time in patients treated with chemotherapy in combination with radiotherapy. However, most enrolled patients were treated with D1 dissection (5). In this context, the ARTIST study, performed to evaluate the usefulness of adjuvant

chemoradiotherapy in patients treated with the standard D2 dissection, is interesting (6).

The 53.2-month follow-up data from the ARTIST study revealed that the treatment completion rate was 75.4% in the XP arm and 81.7% in the XP/XRT/XP arm. While the XP/XRT/XP therapy was shown to be highly tolerable, no prolonged disease-free survival (DFS), the primary endpoint, was unfortunately demonstrated in this treatment arm. Although the subset analysis showed the DFS was longer in lymph node positive patients in the XP/XRT/XP arm, the ARTIST study has certain limitations.

First, do patients with stage IB or II cancer treated with D2 dissection really require chemoradiotherapy? These patients may be overtreated with postoperative chemoradiotherapy. Sasako and colleagues reported a 5-year DFS of 79.2% in patients with stage II cancer treated with D2 dissection followed by S-1 monotherapy only for 1 year (7). Japanese epidemiological data showed the 5-year survival rate from 80% to 90% in patients with stage IB cancer with the primary lesion in the gastric antrum and body (8).

Second, was XP appropriate adjuvant chemotherapy? The treatment completion rate was 81.7% in the XP/XRT/XP arm; however, grade 3 or higher adverse reactions were reported at much higher frequencies in the study arms compared with in patients with advanced gastric cancer treated with XP therapy (with CDDP at 80 mg/m<sup>2</sup>) in the ML17032 study reported by Kang and colleagues (9).

Based on the greater usefulness of XELOX therapy compared with adjuvant chemoradiotherapy reported by Bang and colleagues and the greater usefulness of EOX for advanced esophagogastric cancer compared with ECX suggested by Cunningham and colleagues (10), the combination of XELOX and XP therapy may be more desirable than XP alone. The combined XELOX and radiotherapy was more useful as a preoperative treatment for rectal cancer compared with adjuvant chemotherapy. A nonclinical study reported that oxaliplatin and radiotherapy upregulated thymidine phosphorylase, which

No potential conflict of interest.

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Submitted Feb 23, 2012. Accepted for publication Feb 16, 2012.

Available at [www.amepc.org/tgc](http://www.amepc.org/tgc)

ISSN: 2224-4778

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converts capecitabine to 5FU in the tumor, suggesting a greater antitumor effect compared with other treatment (13,14).

Thirdly patients with diffuse type histology have poor outcome in N0116 study (15), in which chemoradiation benefited all subsets with the exceptions of women and diffuse histology. It is obvious that no selection by histopathology, in other words, not excluding diffuse histology might have negative impact on this study.

Finally, was the duration of treatment appropriate? XP and XP/XRT/XP were used for 18 weeks in the ARTIST study. Adjuvant S-1 was used for 1 year in the study performed by Sakamoto and colleagues (3). A JCOG study is about to start to determine the Optimal Period of Adjuvant S-1 (OPAS-1, JCOG1104, UMIN000007306), to confirm non-inferiority of 4 courses (24 weeks) of S-1 adjuvant chemotherapy to 8 courses (1 year) of the same regimen in relapse-free survival in patients who underwent D1+/D2 gastrectomy and were diagnosed pathologically with stage II gastric cancer. Bang and colleagues used the XELOX therapy for 6 months. Whether the 6-month duration is recommended as it is for the adjuvant chemotherapy for colon cancer should be considered (4).

At any rate, the ARTIST study was definitely underpowered. The doctors should attempt another study based on a new protocol with more appropriate selection of patients, concomitant chemotherapy, and duration of treatment. May the ARTISTS play a beautiful harmony with perioperative chemoradiotherapy in patients with gastric cancer to complete the Schubert Sinfonie Nr. 7 in h moll D. 759 "Die Unvollendete".

## Acknowledgements

We thank Prof. Mitsuru Sasako and Mr. Akio Ohtera for their scientific advices.

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**Cite this article as:** Sato T, Ishii H, Sakai D, Doki Y, Mori M. Can the ARTISTS complete the Schubert Unfinished (Sinfonie Nr. 7 in h moll D. 759 "Die Unvollendete")? *Transl Gastrointest Cancer* 2012;1:117-118. DOI: 10.3978/j.issn.2224-4778.2012.02.02