Editorial Commentary

Delay in initiation adjuvant S-1 monotherapy for gastric cancer: important prognostic factor

Stefan Paul Mönig, Marco Augusto Bonino

Service de chirurgie viscéral, Hôpitaux Universitaires de Genève, Geneva, Switzerland

Correspondence to: Prof. Stefan Paul Mönig. Service de Chirurgie viscéral, Hôpitaux Universitaires de Genève, Rue Gabrielle-Perret-Gentil 4 1205, Geneve, Switzerland. Email: Stefan.Moenig@hcuge.ch.

Provenance: This is an invited article commissioned by our Academic Editor Dr. Zhiming Ma (Division of Gastrointestinal Surgery, Department of Surgery, The Second Hospital of Jilin University, Changchun, China).

Comment on: Nakanishi K, Kanda M, Ito S, *et al.* Delay in initiation of postoperative adjuvant chemotherapy with S-1 monotherapy and prognosis for gastric cancer patients: analysis of a multi-institutional dataset. Gastric Cancer 2019. [Epub ahead of print].

Received: 19 June 2019; Accepted: 25 July 2019; Published: 23 August 2019.

doi: 10.21037/tgh.2019.07.03

View this article at: http://dx.doi.org/10.21037/tgh.2019.07.03

According to the data of the GLOBOCAN cancer observatory of the World Health Organization (WHO) (1) the incidence of gastric tumours in 2018 worldwide was evaluated on 1,033,701 people [1006270–1061880] that means about 5.72% of all the tumours and a mortality evaluated on 782,685 people [738321–829715] making the gastric tumour at the third position as cause of death related to cancer just after lungs and Colorectal tumours. Due to the demographic change, even if we expect a relative decrease of gastric cancer in the western world, the WHO estimates an increase all over the world from 2018 to 2040 of the incidences of this tumour of 70.1% with an expected incidence on 2040 of 1,758,810 peoples (2). Worldwide the incidence of gastric tumour is higher in eastern counties (3) especially Mongolia where the age standardized rate (ASR) is up to 25:100,000, Bhutan (ASR: 18.9:100,000), China (ASR: 17.5:100,000). A well-known theory asset that this distribution of the Upper GI neoplasms is mainly due to the habit in those regions to consume very hot food making a direct damage on the mucosa.

For that reason, we read with great interest the contribution by Nakanishi *et al.* (4), which reported a well written multicentric retrospective study trying to answer if the delay from the surgery to the start of an adjuvant S-1 monotherapy have an impact on the relapse-free survival (RFS) and disease-specific survival (DSS).

The results of this study are relevant, even if the design is retrospective, because, as the authors say, it would be unethical to design a randomized trial as the chemotherapy must be started as soon as possible.

The main two questions about adjuvant S-1 monotherapy are focuses on the ideal duration of the treatment and if a delayed start of the treatment, due mainly to postoperative complications, may influence the outcomes. The first question has been answered from a randomized control trial that concluded that the outcomes of a 6-month adjuvant S-1 monotherapy are significatively worst in term of RFS and DSS than a 12 months treatment. For that reason, the gold standard remains a 1-year treatment. The second question is more controversial as there are two monocentric retrospective studies from Korea, including 840 patients (5), and from Japan, including 113 patients (6), showed that delayed treatment of adjuvant chemotherapy after 6–8 weeks had worse survival outcomes than earlier treatment initiation. Another Japanese retrospective study (7) shows that the delay of more than 6 weeks of an adjuvant S-1 monotherapy of more than 6 months does not impact on the overall survival rate in stage II–III gastric cancer. But if we analyse better the article, we can see that analysing only the treatment with a duration longer than 6 months the difference returns to be significative ($P<0.0001$).

This study was performed analysing the medical records of nine Japanese institutions and reviewing patients who underwent gastrectomy between January 2010 and December 2014. There were included in the study 401 patients that did not receive a neo-adjuvant treatment, that

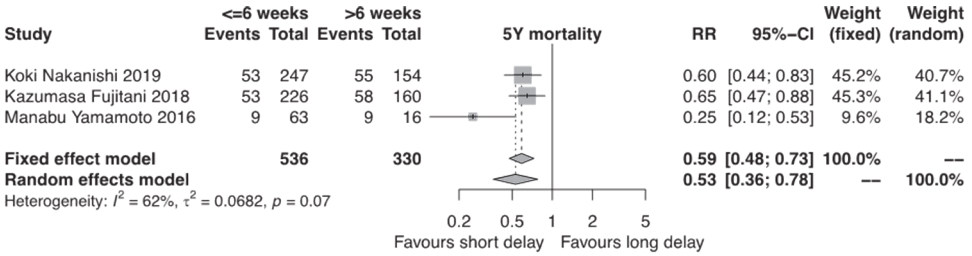

Figure 1 Forest-plot about adjuvant S-1 monotherapy with beginning of the treatment within or after 6 weeks.

underwent a standard D2 R0 gastrectomy, pStage II/III (excluding T1N2/3 and T2N0) and without adverse events to the S-1 therapy within 6 months.

The patients were divided into three main groups depending on the delay of the first administration of the chemotherapy after the surgery: within 6 weeks, between 6 and 8 weeks and after 8 weeks. The average time to the first administration was 5.1±0.9, 7.4±0.5, and 11.9±3.3 weeks. The duration of the administration was 1 year for 77.3% of the patients, 91 patients underwent a recurrence before the end of the adjuvant treatment. Analysing the composition of the population inside the groups we find that, as expected, patients with S-1 administration after 8 weeks had a significantly greater proportion of elderly patients, differentiated type of tumor histology, higher incidence of postoperative complications (especially of Dindo III complications), and longer hospital stay after surgery.

The results show significative better results in terms of RFS and DSS if the treatment is started within 6 weeks then if it is started after 8 weeks. The 5-year RFS was 64.2% in the group with a delay within 6 weeks and 50.2% in the group with a delay longer than 8 weeks (P=0.004). The 5-year DSS was 78.6% in the group with a delay within 6 weeks and 53.2% in the group with a delay longer than 8 weeks (P=0.0003).

The univariate analysis for relapse identified different predictive factors for RFS but after performing a multivariate analysis the authors identified the following risk factors: tumour size ≥5.0 cm (P=0.0458), pStage III (P<0.0001), and the administration of the chemotherapy after 8 weeks from the surgery (P=0.0069). The main independent risk factor of a delayed beginning of the adjuvant therapy seems to be the postoperative complications. A subgroup analysis shows that the longer delay to the start of the S-1 chemotherapy was an even more important risk factor in males, patients with tumour size ≥5.0 cm, tumour differentiation and pStage III.

Moreover, the analysis of the first recurrence site shows that the cumulative rate of hematogenous recurrence was increased significantly in delayed chemotherapy (7.3% in the <6 weeks group *vs*. 21% in the >8 weeks group, P=0.0003).

Combination postoperative adjuvant chemotherapy for gastric cancer, such as capecitabine plus oxaliplatin, has been reported to significantly suppress hematogenous metastasis and it had a better effect than S-1 monotherapy in pStage III patients (8). For those reasons the authors suggested, in the case of delayed adjuvant chemotherapy, to choose a strong chemotherapy regimen or to choose postoperative S-1 monotherapy with for a longer duration.

A meta-analysis of the literature about adjuvant S-1 monotherapy with beginning of the treatment within or after 6 weeks shows, also if the with a heterogeneity of 62%, a benefit of an early beginning of the treatment (within 6 weeks) in terms of 5 years mortality as shown in *Figure 1*.

In summary we agree with the conclusions of this article and the importance to start the treatment as soon as possible. Further research should be performed to better understand the correct treatment strategy to adopt in the patient where an early beginning of the S-1 monotherapy is not feasible due to the general postoperative condition of the patient and postoperative complications.

Moreover, use of adjuvant chemoradiotherapy could be take in consideration in those patients with a higher risk of recurrence (extensive node-positive disease after resection, not completed D2-node-dissection and/or less than 25 nodes removed, R+ resection). In those cases, a protocol in conformity with the Korean Phase III ARTIST study (9) should be a good option.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. WHO. Cancer Today. Estimated number of new cancers in 2018, worldwide, both sexes, all ages. Available online: https://gco.iarc.fr/today/online-analysis-table
2. WHO. Cancer Today. Estimated number of incident cases from 2018 to 2040, stomach, both sexes, all ages. Available online: https://gco.iarc.fr/tomorrow/graphic-isotype?type=0&population=900&mode=population&sex=0&cancer=39&age_group=value&apc_male=0&apc_female=0
3. WHO. International Agency for Research on Cancer. Cancer fact sheets. Stomach cancer. Available online: https://gco.iarc.fr/today/data/factsheets/cancers/7-Stomach-fact-sheet.pdf
4. Nakanishi K, Kanda M, Ito S, et al. Delay in initiation of postoperative adjuvant chemotherapy with S-1 monotherapy and prognosis for gastric cancer patients: analysis of a multi-institutional dataset. Gastric Cancer 2019. [Epub ahead of print].
5. Park HS, Jung M, Kim HS, et al. Proper timing of adjuvant chemotherapy affects survival in patients with stage 2 and 3 gastric cancer. Ann Surg Oncol 2015;22:224-31.
6. Yamamoto M, Sakaguchi Y, Kinjo N, et al. S-1 Adjuvant Chemotherapy Earlier After Surgery Clinically Correlates with Prognostic Factors for Advanced Gastric Cancer. Ann Surg Oncol 2016;23:546-51.
7. Fujitani K, Kurokawa Y, Takeno A, et al. Time to initiation or duration of S-1 adjuvant chemotherapy; which really impacts on survival in stage II and III gastric cancer? Gastric Cancer 2018;21:446-52.
8. Bang YJ, Kim YW, Yang HK, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet 2012;379:315-21.
9. Park SH, Sohn TS, Lee J, et al. Phase III Trial to Compare Adjuvant Chemotherapy With Capecitabine and Cisplatin Versus Concurrent Chemoradiotherapy in Gastric Cancer: Final Report of the Adjuvant Chemoradiotherapy in Stomach Tumors Trial, Including Survival and Subset Analyses. J Clin Oncol 2015;33:3130-6.

doi: 10.21037/tgh.2019.07.03
Cite this article as: Mönig SP, Bonino MA. Delay in initiation adjuvant S-1 monotherapy for gastric cancer: important prognostic factor. Transl Gastroenterol Hepatol 2019;4:61.

