What Platform Regimens are Clinically Beneficial in Chemotherapy for Colorectal Cancer?

Akihito Tsuji*
Department of Medical Oncology, Kobe City Medical Center General Hospital, Japan

EDITORIAL

Since the report by Tournigand [1], both CPT-11 and LOHP have been described in the National Comprehensive Cancer Network (NCCN) Guidelines [2], European Society for Medical Oncology (ESMO) 2013 Guidelines [3], and the Japanese guidelines [4] as standard chemotherapies for colorectal cancer, and both have been used. However, which platform regimen produces the best therapeutic effects has yet to be resolved, as is the investigation on whether to adopt one of the anti-EGFR antibody drugs or one of the anti-VEGF antibody drugs as the molecular target drug of choice to be used in combination with the primary chemotherapy. Currently, the WJOG4407 trial [5] is underway to examine which of FOLFOX or FOLFIRI is desirable as combination therapy with an anti-VEGF agent in primary treatment, and depending on the outcome, a substantial treatment strategy change is anticipated.

Under these circumstances, platform regimens are often chosen over others in clinical practice based on differences in toxicity profiles. Stated more concretely, this means according to the patients' tolerances for toxicities, including alopecia, diarrhea, and neurotoxicity, if there is generally not much difference in their effects and toxicity. Moreover, regimens that concurrently use CPT-11 and LOHP, such as the FOLFOXIRI regimen, have also recently emerged [6]; however, many issues remain to be resolved before they can be accepted as standard platform regimens, including high toxicity and as yet undetermined molecular target drug combinations.

Therefore, in order to determine which platform regimen is more favorable, LOHP-based or CPT-11-based, at this moment when their effects and toxicity have not as yet exhibited much difference, recommendations in view of their clinical advantages are necessary.

Choice of treatment based on the properties of LOHP is an example. Because of its accumulative neurotoxicity, LOHP, if used as late-line treatment, has drawbacks in that drug withdrawal or changes in therapy are difficult to carry out when its neurotoxicity has risen to an unacceptable level. If LOHP is used as front-line treatment, on the other hand, switching LOHP to the stop-and-go strategy [7] or the CPT-11-based regimen is possible; therefore, the use of LOHP as primary therapy is recommended. Furthermore, with LOHP there is an allergic reaction issue. If the LOHP-based regimen is used as front-line treatment, it is possible to continue the platform regimen without LOHP and subsequently switch to the CPT-11-based regimen in case an allergic reaction is experienced. However, if the CPT-11-based regimen is used as front-line treatment and the LOHP-based regimen as second-line treatment, and if an allergic reaction to LOHP is experienced, continued treatment with the regimen not containing LOHP would be unlikely to provide much benefit because it would already have been used as primary therapy. For patients undergoing treatment, allergic reactions are not only a distressing form of toxicity but also one that can lead directly to abrupt cessation of treatment. In order to avoid this, it is advisable to use the LOHP-based platform regimen as front-line treatment [8,9].

There is also the issue of treatment lines when an anti-EGFR antibody drug is used concurrently as front-line therapy. In this case, if FOLFIRI + an anti-EGFR antibody drug were to be given as front-line treatment, the second-line treatment would be FOLFOX + an anti-VEGF antibody drug, and subsequently, a new drug such as regorafenib. If FOLFOX + an anti-EGFR antibody drug were to be given as front-line treatment, however, FOLFIRI + an anti-VEGF antibody drug would be chosen as secondary therapy, and as tertiary therapy, CPT-11 + an anti-EGFR antibody drug [10], if the patient is refractory to CPT-11, or anti-EGFR antibody rechallenge [11] would be considered; since this is followed by the new drug, such as regorafenib, starting with FOLFOX would allow us to choose an extra treatment line.

On the other hand, if CPT-11 precedes LOHP, it would offer substantial benefits including delay in the risk of prolonged neurotoxicity due to LOHP accumulation and thereby to better maintenance of the patient’s quality of life.

Taking these points into consideration, for the present, we should decide on the platform regimen for the primary therapy and await future study results. In particular, even though the
progression-free survivals are equal depending on how the chemotherapy regimens are combined, the order in which the regimens are administered may account for differences in the extent of overall survival prolongation.

Whereas for the mutated form of RAS the results of the aforementioned WJOG4407 trial will likely determine its platform regimen for primary therapy, for the wild type a review of clinical merits and demerits will likely be required after the results of not only the WJOG4407 trial but also the CALGB 80405 trial [12], examining the optimal combination therapy as primary therapy, an anti-EGFR antibody drug or an anti-VEGF antibody drug, become available.

REFERENCES


5. View of UMIN CTR Clinical Trail registration information.


12. Cetuximab and/or Bevacizumab Combined With Combination Chemotherapy in Treating Patients With Metastatic Colorectal Cancer.