Neoplasma 2024; 71(4): 415–416

doi:10.4149/neo_2024_240618N262-R

A response to: Artificial immortalization, number of therapy lines, and survival of patients with advanced gastric and esophagogastric adenocarcinoma

Letter

Received August 2, 2024 / Accepted August 9, 2024

Dear Editor,

We thank Krečak, Skelin, and Lucijanić for their interest in our recently published article on the impact of the number of therapy lines on survival in advanced gastric (GC) and esophagogastric (EGJ) adenocarcinoma [1]. In this retrospective study, we confirmed the positive impact of the number of chemotherapy lines on overall survival (OS). Therefore, patients treated with 3 or more therapy lines had the longest median OS of 20 months, although the median OS of the whole cohort was only 11.0 months.

Krečak, Skelin, and Lucijanić suggest that the results of our study may represent immortalization bias as patients with more therapy lines lived long enough to reach later treatment lines. Indeed, the observation of improved OS in cancer patients receiving more lines of therapy could be misleading due to immortalization or survivorship bias. Immortalization bias occurs when patients who live longer naturally have more opportunities to receive additional lines of therapy. This can create a false impression that more lines of treatment or more drugs given are directly causing improved survival, when in reality, it may be that patients with better prognoses or more indolent diseases are simply able to survive long enough to receive more treatments. When analyzing retrospective data or observational studies, such as our study, patients who receive multiple lines of therapy inherently must have survived long enough to do so. This can lead to an overestimation of the benefit of later lines of treatment, as the comparison group may include patients who died earlier due to more aggressive disease or poorer overall health. Consequently, treatments appear more effective than they truly are due to immortalization bias, it may result in the overuse of certain therapies or misallocation of resources.

Several confounding factors, such as patient selection, tumor biology, and treatment response, can contribute to this bias. Of course, clinicians should be cautious when interpreting studies showing improved OS with multiple lines of therapy, especially if they are not randomized controlled trials. To mitigate immortalization bias, carefully designed prospective randomized controlled trials are crucial. These trials can help isolate the true effect of additional lines of therapy by ensuring that patient characteristics are balanced between treatment arms. While real-world data can provide valuable insights, it's particularly susceptible to immortalization bias. Researchers should use appropriate statistical methods, such as landmark analysis or time-dependent modeling, to account for this bias when analyzing observational data.

In conclusion, while additional lines of therapy may and do provide benefit to some patients, the apparent improvement in OS associated with more lines of treatment could be significantly influenced by immortalization bias. This underscores the importance of critical evaluation of study designs and results, as well as the need for well-designed prospective trials to accurately assess the true impact of multiple lines of therapy on patient outcomes [2]. Nevertheless, real-world data is a cornerstone of medical knowledge and absolutely should and must be collected and reported to define the impact of new drugs and therapies as well to define the optimal treatment strategies for real-world patients.

To at least partially mitigate the problem of immortalization bias in our study, we calculated the OS from the start of second and third-line therapy. Besides that, we would like to emphasize that despite the rising proportion of progressive disease with the number of therapy lines, 55.1% of patients in the first line, 45.8% in the second, and 25.7% of patients in the third or more lines had defined benefit of therapy (response or stable disease). The benefit of one therapy line enabled the application of a subsequent therapy line after progression in case of preservation of good general condition. Optimization and personalization of therapy in every patient case is of paramount importance and the number of lines of treatment should be as optimal as possible for every single patient. There is no doubt that more patients should receive more therapies and that there is a correlation between outcomes on the institutional level between the quality of oncological care, outcomes, and the number of treatment lines given.

In our study, we confirmed the observations of similar studies in other cohorts that the challenges of the treatment of advanced GC and EGJ cancer are the short duration of the response to the treatment frequently accompanied by a rapid deterioration of

the patient's general condition and steep attrition rates between therapy lines [3].

We strongly agree that novel, more effective drugs and their combinations are needed especially in the first line, but also in subsequent therapy lines to improve substantially the median OS of patients with advanced GC and EGJ cancer.

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