Trastuzumab Beyond Progression in Retrospective Analyses: An Issue of Equal Opportunities

FILIPPO MONTEMURRO, STEFANIA REDANA, ELENA GEUNA, ANDREA MILANI, VALENTINA ROSSI,
ROSSELLA MARTINELLO, GIORGIO VALABREGA, MASSIMO AGLIETTA

Fondazione del Piemonte per l'Oncologia/Division of Medical Oncology I, Institute for Cancer Research and Treatment (IRCC), Torino, Italy

Disclosures: Filippo Montemurro: *Consultant/advisory role:* GlaxoSmithKline S.P.A.; *Honoraria:* GlaxoSmithKline S.P.A.; Stefania Redana: None; Elena Geuna: None; Andrea Milani: None; Valentina Rossi: None; Rossella Martinello: None; Giorgio Valabrega: None; Massimo Aglietta: None.

The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. No financial relationships relevant to the content of this article have been disclosed by the independent peer reviewers.

We read with great interest the retrospective study published by Extra et al. [1] in *The Oncologist* and the accompanying editorial [2]. In particular, the analysis of patients continuing trastuzumab beyond disease progression was intriguing because of the inclusion of a control group of patients stopping trastuzumab at or just before disease progression. The authors correctly pointed out that the baseline prognostic profile of patients discontinuing trastuzumab was worse than that of patients in the continuation group. This introduced an obvious bias toward better clinical outcomes in patients continuing trastuzumab. However, we believe that the striking difference in the median survival times from the date of first progression (21.3 months versus 4.6 months) favoring patients continuing trastuzumab must have a more severe underlying bias. In a similar analysis that we published in *The Oncologist* in 2006, we could not find significant differences in clinical outcomes according to whether trastuzumab was continued or stopped in patients progressing during an initial trastuzumab-based regimen [3]. In particular, we observed that the median survival time from the date of first progression (henceforth, postprogression survival) for 40 patients continuing trastuzumab was

21.0 months, which is similar to that reported by Extra et al. [1]. However, 71 patients stopping trastuzumab and receiving additional anticancer therapy experienced a median postprogression survival interval of 18.7 months (Fig. 1). Notably, we identified two further groups of patients who did not continue trastuzumab beyond progression. Fourteen patients had experienced unacceptable trastuzumab-related toxicity leading to treatment discontinuation before progression. When disease progression occurred, they were not retreated with this monoclonal antibody. Another 21 patients experienced rapid progression during first-line trastuzumab-based therapy and were unable to receive additional anticancer therapy, but just supportive care. The median postprogression survival durations in the former and latter groups of patients were 7.8 months and 2.4 months, respectively (Fig. 1).

We excluded from our analysis these two groups of patients. In fact, a fair comparison of clinical outcomes to evaluate the hypothesis that continuing trastuzumab beyond progression is beneficial over no continuation requires that patients in the “control” group have “equal therapeutic opportunities” to patients in the “experimental”

Correspondence: Filippo Montemurro, M.D., Fondazione del Piemonte per l'Oncologia/Division of Medical Oncology I, Institute for Cancer Research and Treatment (IRCC), Strada Provinciale 142, Km 3.95, 10060 Candiolo, Torino, Italy. Telephone: 0039-011-9933251; Fax: 0039-011-9933299; e-mail: filippo.montemurro@ircc.it Received October 1, 2010; accepted for publication February 9, 2011; first published online in *The Oncologist Express* on March 10, 2011. ©AlphaMed Press 1083-7159/2011/\$30.00/0 doi: 10.1634/theoncologist.2010-0329

Figure 1. Kaplan–Meier estimates of survival from the date of first progression in patients continuing trastuzumab beyond disease progression (black solid line), stopping trastuzumab and receiving additional anticancer therapy (black dashed line), stopping trastuzumab because of toxicity (grey solid line), and receiving only supportive care because of progression (grey dashed line).

group. For patients experiencing prohibitive toxicity with trastuzumab or eligible for supportive care only, continuing trastuzumab beyond progression and, probably, receiving optimal anticancer treatment were not suitable therapeutic opportunities. Indeed, the clinical outcome of these patients was dismal, as described above.

We noted that “stopping trastuzumab” was the only requirement described in patients in the control group of the Hermine study. We, therefore, went back to our original dataset and reanalyzed data using this same definition. All 106 patients stopping trastuzumab were compared with patients continuing trastuzumab beyond disease progression (Fig. 2). Survival from the date of first progression for patients continuing trastuzumab beyond disease progression was about 10 months longer than for those stopping trastuzumab (21.0 months versus 10.6 months; $p = .03$).

We subsequently analyzed a comparison population including only those patients who could not receive trastuzumab because of prior toxicity or rapid disease progression (35 patients) (Fig. 3). In this case, patients stopping trastuzumab had a median postprogression survival duration of 3.7 months ($p < .01$), a finding that is remarkably similar to what was reported by Extra et al. [1]. We, therefore, argue that the dismal median postprogression survival time reported for the Hermine study (4.6 months) may not be a result of stopping trastuzumab. A more likely explanation is that a proportion of patients stopping trastuzumab could not go on to receive optimal anticancer therapy.

Based on these considerations, it would be interesting if

Figure 2. Kaplan–Meier estimates of survival from the date of first progression in patients continuing trastuzumab beyond disease progression (solid line) or stopping trastuzumab (dashed line) (see text for details for the comparison group).

Figure 3. Kaplan–Meier estimates of survival from the date of first progression in patients continuing trastuzumab beyond disease progression (solid line) or stopping trastuzumab (dashed line) (see text for details of the comparison group).

Extra and colleagues could reanalyze their data by distinguishing patients stopping trastuzumab according to whether or not they had “equal opportunities” to patients continuing trastuzumab beyond progression.

Editor’s note: Dr. Extra was invited to reply but declined comment.

AUTHOR CONTRIBUTIONS

Conception/Design: Filippo Montemurro

Provision of study material or patients: Stefania Redana, Andrea Milani, Valentina Rossi, Rossella Martinello

Collection and/or assembly of data: Elena Geuna, Valentina Rossi, Rossella Martinello

Manuscript writing: Filippo Montemurro

Final approval of manuscript: Stefania Redana, Elena Geuna, Andrea Milani, Valentina Rossi, Rossella Martinello, Giorgio Valabrega, Massimo Aglietta

REFERENCES

- 1 Extra JM, Antoine EC, Vincent-Salomon A et al. Efficacy of trastuzumab in routine clinical practice and after progression for metastatic breast cancer patients: The observational Hermine study. *The Oncologist* 2010;15:799–809.
- 2 Yerushalmi R, Gelmon K. Treatment beyond progression: Is it moving from belief to evidence? *The Oncologist* 2010;15:796–798.
- 3 Montemurro F, Donadio M, Clavarezza M et al. Outcome of patients with HER2-positive advanced breast cancer progressing during trastuzumab-based therapy. *The Oncologist* 2006;11:318–324.