25BP Incidence of clinically significant toxicities in patients with high endoxifen concentrations

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Background: Tamoxifen is essential in the treatment of estrogen receptor positive breast cancer. Concentrations of its active metabolite endoxifen > 3.97 ng/mL have been associated with a 26% lower recurrence rate in the adjuvant setting (Madlensky 2011), providing a rationale for therapeutic drug monitoring. However, the risk of high endoxifen concentrations has not been established. Therefore, we investigated whether extremely high endoxifen levels are correlated with a higher incidence of clinically significant toxicities.

Methods: Patients receiving adjuvant tamoxifen treatment (20 mg) with a steady state endoxifen level above 25 ng/mL were retrospectively identified in databases of the CYPTAM study (n = 667, NTR 1509) and of samples collected in routine care (n = 1768). The percentage of patients with clinically significant toxicities, defined as toxicities leading to either dose reduction or treatment discontinuation, was compared to the overall tamoxifen population. As historical comparison, studies described in the EBCCTG overview (2011) in which patients received adjuvant tamoxifen (20 mg) and which reported clinically significant toxicities were selected.

Results: 26 patients (1.5%) had an endoxifen level > 25 ng/mL, of which 4 patients (15%) had clinically significant toxicities, compared to 10.2% in the overall tamoxifen population (p = 0.39, weighted average of 10 clinical trials, n = 9688, Baum (2002), Margolese (2016), Chirgwin (2016), Morales (2007), Bartlett (1987), Colleoni (2006), Bonneterre (2001), Kaufmann (2005), Bramwell (2010), Tevaarwerk (2014)). Reported toxicities were mood disturbances (n = 3), hot flushes (n = 2) and musculoskeletal disorders (n = 1). Median time on treatment was 28 months in patients with high endoxifen levels, compared to 47 months reported in literature.

Conclusions: The incidence of clinically significant toxicities is relatively low and is similar in patients with extremely high endoxifen levels and the overall tamoxifen population. Therefore, dose reductions are not indicated in patients with high endoxifen concentrations without toxicity.

Clinical trial identification: CYPTAM study: NTR 1509 (release date 27 October 2008).

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