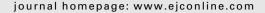


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Editorial Comment

The anthracycline-trastuzumab interaction: Up-regulated binding may provide vital mechanistic insight

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Cardiotoxicity of anticancer treatment has been a concern for more than three decades. Throughout most of this time the concern focused on the anthracyclines, where cumulative-dose related toxicity associated with typical cardiac biopsy changes and a sometimes progressive cardiomyopathic course became a well recognised entity. Risk factors were recognised, preventive strategies evolved, and cardiac monitoring became routine. While these strategies helped to reduce the morbidity of anthracycline-associated cardiotoxicity, not infrequently severe myopathy was encountered, and occasionally refractory congestive heart failure and cardiac death was seen.

The finding that cardiotoxicity also existed with the anti-HER 2 monoclonal antibody trastuzumab, initially reported by Slamon and colleagues, was unexpected. Especially surprising was the fact that 27% of patients exposed to the agent during the pivotal trials had measurable cardiotoxicity. Slamon's report raised considerable concern and ultimately provided, at least in part, the impetus to include extensive cardiac monitoring for patients enrolled in clinical trials designed to examine the oncologic efficacy of trastuzumab. Criticism was voiced by some as to the advisability of exposing patients who were to be treated in the adjuvant setting to trastuzumab, especially when combined in regimens that also contained an anthracycline.

Questions were raised regarding possible mechanisms of this phenomenon: was it caused by inherent de novo cardiotoxicity, and if so how? To what extent did prior or concomitant exposure to anthracyclines, agents with well known biopsy-proven sub-clinical cardiac damage play a role; and finally, was the high incidence of toxicity demonstrated by Slamon, at least in part, a surveillance artifact attributable to the sub-optimal predictive value of parameters of systolic dysfunction, and in part to broad, possibly over-inclusive clinical thresholds used in the trial.⁵

Over the years some of the questions have been answered: as it turned out, sequential cardiac stresses almost certainly do play a role. Anthracycline-induced cell death that may not have reached the extent that it can be readily appreciated on routine ejection fraction testing does predispose the heart for a clinically manifest course when the organ is sequentially stressed, even though that sequential stress, in this case in the form of trastuzumab, might have been otherwise well tolerated. Additionally, trastuzumab does exhibit inherent or per se cardiotoxicity, albeit of a type that is qualitatively quite different from that typically seen with the anthracyclines; the damage does not cause the typical biopsy changes seen with the anthracyclines. Perhaps the greatest distinguishing factors between anthracycline and trastuzumab toxicity is that the cardiac dysfunction associated with trastuzumab has a much greater likelihood to be reversible, and that it probably does not cause the same degree of cell death as do the anthracyclines. The form of cardiotoxicity associated with trastuzumab, and probably with several other newer agents, is

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now Referred to as type II treatment-related cardiac dysfunction. A question that has eluded clarification relates to the extent of cardiac damage in the Slamon pivotal trial study: why was it as high as it was, when the subsequent reports of cardiotoxicity in the four large adjuvant trials were all in the range of 5%?

A hint as to what might be taking place can be found in the cardiac data of the HERA trial, the study among the four that had the lowest incidence of cardiotoxicity, estimated at 0.5% compared with about 5% in the other three trials.7 Interestingly the patient data relevant to cardiotoxicity in the HERA differed in at least two ways from that of the NSABP B-31 trial, the BCIRG-006 trial, and the Intergroup trial: first the HERA study stipulated a post-anthracycline ejection fraction of 55% or more, while the others had a lower pre-trastuzumab ejection fraction value of 50% as the cutoff; if sequential stress plays an important role, less baseline anthracycline damage might account for some of the difference. The other distinguishing characteristic of the HERA population is that there was a longer time interval between when patients finished chemotherapy and when they started trastuzumab. In HERA the mean time interval was 89 days, much longer than in the other trials; the true importance of this time difference may have been heretofore greatly underappreciated.

The article by de Korte and colleagues in the present issue of European Journal of Cancer provides a new perspective on this importance difference, and helps explain this apparent enigma.8 We know, for example, that oxidative stress plays a role in anthracycline cardiotoxicity, and, as Timolati and colleagues have demonstrated, that HER 2 modulates oxidative stress in the heart.9 The preliminary interpretation of the de Korte study is that, at least in some patients who have been treated with anthracyclines, the HER 2 receptor is upregulated to allow the demonstrated binding by trastuzumab to be visualised; blocking this receptor with trastuzumab may play an important role in the synergistically additive toxicities of anthracycline and trastuzumab. The Slamon data gains new importance through this demonstrated up-regulation. If enhanced trastuzumab binding to the cardiac myocyte after anthracycline exposure is confirmed, and if this binding results in impaired cell repair as has been postulated, an important piece of this heretofore unexplained puzzle may be, at least in part, elucidated.

The present study involved only a small group of patients and will need confirmation. Additionally, the study leaves some very important questions unanswered: first, is the binding anthracycline specific, or is this a phenomenon that is related to acute cell injury as may be seen in other forms of increased acute oxidative stress or acute myocyte damage? If so, then myocarditis of other etiologies may turn out to be risk factors for trastuzumab administration that have yet to be appreciated. Another important question relates to the duration of trastuzumab binding in the face of anthracycline

exposure; such knowledge would be of fundamental importance in the timing of sequential regimens that employ both an anthracycline and trastuzumab. Additionally, the question begs as to whether there is increased binding of trastuzumab in tumour cells, and, if so, what are the oncologic implications of the timing of sequential regimens: might we protect the tumour as well as the heart by delaying sequential treatment?

Notwithstanding these remaining questions, the de Korte paper is a wonderfully stimulating bit of research, one that hopefully will open a number of doors to provocative and exciting future studies.

Conflict of interest statement

The author is a consultant for Supratech (Canada), Glaxo-SmithKline, Genentech and F. Hoffinann-La Roche and is also on the speakers' bureau for GlaxoSmithKline.

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