**Fcy Receptor Predictive Genomic Testing and the Treatment of Indolent Non-Hodgkin Lymphoma**

In this month’s edition of Clinical Lymphoma, Myeloma & Leukemia, Zhuang et al provide an insightful review on the affect that polymorphic variants in Fcγ receptors (FcγRs) play in predicting response outcome in patients with non-Hodgkin lymphoma (NHL) who receive rituximab therapy.¹ The paper nicely outlines the potential role and limitations of predictive genomics involving FcγR polymorphisms (Figure 1). Since the report by Cartron et al in 2002 showing that polymorphisms in FcγRII/1A-158 were associated with response to rituximab in patients with follicular NHL, a number of interesting queries have arisen on just how polymorphic FcγR testing could be used in the real-world practice of hematologists and oncologists.² These queries have included:

1. In what B-cell malignancies do FcγRs polymorphisms influence rituximab response and progression-free survival (PFS)?
2. Which FcγR polymorphisms are important?
3. Which FcγR polymorphic variants predict response?
4. What role can FcγR predictive testing play in determining rituximab-based therapy?

Among the B-cell malignancies, supportive data demonstrating a role for FcγR polymorphic test in predicting rituximab response has so far been established only for the indolent NHL diseases, including follicular NHL and Waldenström macroglobulinemia (WM).³,⁴ Why this is not the case for chronic lymphocytic leukemia (CLL) or aggressive NHLs is unclear, but other factors influencing rituximab response could be contributory. As pointed out by Zhuang et al, among indolent NHL patients, FcγR polymorphisms predict for rituximab monotherapy response and/ or PFS, but their affect in predicting outcome with combination rituximab therapy has been variable.¹ Adding to the debate, a large Southwest Oncology Group (SWOG) study that randomized patients to either CHOP (cyclophosphamide/doxorubicin/vincristine/prednisone) or CHOP plus rituximab (CHOP-R) showed that polymorphisms in FcγRII/1A were highly predictive of PFS among patients receiving CHOP-R but not CHOP.⁵ Hunter et al similarly showed that depth of response and long-term disease control were dependent on FcγRII/1A polymorphisms in patients with WM who received chemoinmunotherapy with rituximab.⁶ The potential affect for polymorphisms in FcγR in determining the outcome of maintenance rituximab therapy was recently shown by Pierz et al, who examined the outcome of patients with follicular NHL who received induction therapy with rituximab and then were randomized to either observation or maintenance rituximab.⁷ These studies showed that patients who expressed FcγRIIIA-158-V/V (valine/ valine) and FcγRIIIA-V/F (valine/phenylalanine) responded better to rituximab induction and maintenance therapy than patients with FcγRIIIA-158-F/F genotype. The affect of polymorphisms in FcγRIIIA-158 has also been investigated in the PRIMA study, wherein patients with indolent NHL receiving chemoimmunotherapy were randomized to observation or maintenance rituximab. Superior PFS was observed for patients receiving maintenance rituximab, and the affect of FcγRIIIA-158 in predicting maintenance response outcome is awaited.⁸

A number of polymorphisms, both in activating and inhibitory FcγR receptors have been investigated for their predictive role in rituximab response. Only polymorphisms at FcγRIIA-131,
Editorial

FCyRIIA-48, and FCyRIIa-158 have been reported to be associated with rituximab response in indolent NHL. The effect of FCyRIIA-131, while validated in some but not other studies, has been questioned as a predictive marker since rituximab is an IgG1 class immunoglobulin, and FCyRIIA-131 is believed to be a determinant of IgG2 but not IgG1 antibody binding. One potential explanation unifying these observations is the tight genetic linkage between FCyRIIA and FCyRII polymorphisms. In a previous edition of Clinical Lymphoma, Myeloma & Leukemia, Hajihrassisi et al demonstrated that polymorphisms in FCyRIIA-131 showed linkage disequilibrium with polymorphisms in both FCyRIIA-48 and FCyRII-158. Others have reported similar results, and have suggested a primacy for FCyRIIA-158 in determining rituximab response outcome in patients with indolent NHL.

A challenging aspect on the use of FCyRIIA-158 receptor polymorphisms is clarifying what exactly is the predictive role for these patients who are heterozygous. Approximately 40%-50% of the North American population is heterozygous for V/V at FCyRIIA-158, while 10%-15%, and 35%-40% of the population are homozygous for V/V and F/F, respectively. In some studies, patients who were FCyRIIA-158-V/V showed outcomes analogous to those patients who were heterozygous for phenylalanine (i.e., FCyRIIA-158-F/V), whereas in other studies these patients demonstrated more robust clinical outcomes in line with patients who were homozygous for valine (i.e., FCyRIIA-158-V/V). In vitro studies, human IgG1 binding by FCyRIIA-158-V/V receptors is intermediate to those of FCyRIIA-158-F/F and FCyRIIa-V/V, though an additional influence by polymorphisms at FCyRIIA-48 may also contribute to binding affinity.

Perhaps the most challenging of all queries is the precise positioning of FCyR polymorphism testing in the care of patients with indolent NHL. At present, only testing for FCyRIIA-158 is cleared by the US Food and Drug Administration. While the obvious use for FCyRIIA-158 polymorphic testing is for identifying indolent NHL patients who are more likely to respond to rituximab, there are a few points considering. Not all patients who exhibit FCyRIIA-158-F/F fail to respond, nor do all patients who express valine at FCyRIIA-158 demonstrate a response to rituximab. In addition, rituximab may also promote anti-tumor activity by other mechanisms including chemosensitization, and possibly induction of secondary immunity. Despite these considerations, there are several important decision trees where FCyRIIA-158 polymorphic testing might be useful in the care of patients with indolent NHL, and deserve greater research efforts: (1) identification of candidates for whom rituximab treatment alone may produce results as good as those in combination with chemotherapy; (2) identification of candidates who are more likely to benefit with maintenance rituximab therapy; (3) identification of candidates who are more likely to respond to non-rituximab-based therapy; (4) identification of candidates who may benefit with alternative antibody-based therapy that is independent of FCyRIIA-158 polymorphisms such as radioimmunotherapy with othebrumomab or ibritumomab tiuxetan, or with newer un conjugated antibodies such as GA101, GA101, a novel glycoengineered anti-CD20 humanized antibody, possesses an Fc domain that exhibits greater indifference to FCyRIIA-158 polymorphisms and also induces direct tumor cell apoptosis versus rituximab; and (5) use in predicting response to other IgG1 class antibodies in patients with indolent NHL such as alemtuzumab and ofatumumab.

In this era of expanding treatment options for patients with NHL and imposing pharmacoeconomics, predictive genomic testing can play an integral role in its care. The use of FCyRIIA-158 polymorphism testing to predict outcomes with agents such as rituximab has the capacity to contribute to the individualized care of patients with indolent NHL, and provide more directed, effective, and possibly cost-effective therapy. Such considerations clearly warrant further exploration of FCyRIIA-158 polymorphism testing in the care of patients with indolent NHL.

Steven P. Treon, MD, MA, PhD

References