

WT1 transcript levels following anthracycline and cytarabine-based chemotherapy predicts a reduced risk of subsequent relapse.

e. Methodology Tip—Should Biomarkers be Measured Before or After Chemotherapy?

The Cilloni study (316) is distinguished from most other studies of oncology biomarkers, in that it found postchemotherapy measurements of a biomarker to have prognostic value. The Cilloni study directly addressed the possibility that prechemotherapy biomarker data might have prognostic value, and discovered they were not useful for this purpose. Penault-Llorca et al. (317) also studied the relative merits of measuring biomarkers before and after chemotherapy. In a study of breast cancer treated by chemotherapy, these authors found that HER2 negativity predicted better survival, and HER2 positivity predicted worse survival, in terms of the endpoint DFS. These authors also conducted their analysis with an endpoint other than DFS, namely, the endpoint of overall survival. Surprisingly, HER2 expression was found to predict overall survival only when HER2 expression was measured after chemotherapy. Where HER2 expression was measured before chemotherapy, there was no difference in overall survival in the HER2-negative patients and in the HER2-positive patients. None of the patients had received trastuzumab (the antibody that targets

HER2). As a general proposition, researchers interested in prognostic markers prefer to use biopsies from chemotherapy-naive subjects, in order to avoid the potentially confounding effects of the therapy on the biomarker. However, the above studies reveal that taking biopsies before, as well as after, chemotherapy might be the most productive approach.

f. Example of Use of MRD—The Grimwade Study Using PML-RAR-Alpha Fusion Protein

Grimwade et al. (318) reveal the utility of collecting data on minimal residual disease during anticancer therapy. Minimal residual disease was measured by assays that detected expression of the mRNA encoding the fusion product, PML-RAR-alpha. Patients with APL were treated with standard chemotherapy, all-trans-retinoic acid. The patients experienced remission. Assays for fusion protein transcript were conducted on bone marrow samples at regular intervals following remission. Where levels of mRNA increased, after remission, and where the remission triggered a finding of minimal residual disease, patients were further treated with preemptive chemotherapy to prevent subsequent clinical remission. Evidence from this study suggested that use of minimal residual disease assays, coupled with preemptive therapy, can reduce subsequent relapse. The data indicated that this approach to treating APL can cut in half the rate of relapse.

³¹⁶Cilloni D, Renneville A, Hermitte F, et al. Real-time quantitative polymerase chain reaction detection of minimal residual disease by standardized WT1 assay to enhance risk stratification in acute myeloid leukemia: a European LeukemiaNet study. *J. Clin. Oncol.* 2009;27:5195–201.

³¹⁷Penault-Llorca F, Abrial C, Mouret-Reynier MA, et al. Achieving higher pathological complete response rates in HER-2-positive patients with induction chemotherapy without trastuzumab in operable breast cancer. *Oncologist* 2007;12:390–6.

³¹⁸Grimwade D, Jovanovic JV, Hills RK, et al. Prospective minimal residual disease monitoring to predict relapse of acute promyelocytic leukemia and to direct pre-emptive arsenic trioxide therapy. *J. Clin. Oncol.* 2009;27:3650–58.