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Molecular Pharmacology, Drug Resistance

#3471 Individualized Tumor Response (ITR) Profiling for Drug Selection in Tailored Therapy: Meta-analysis of 1929 Cases of Leukemia and Lymphoma. Andrew G. Bosanquet, PhD, MRC Path, Gertjan J. Kasper, MD, PhD, Rolf Larsson, MD, Robert A. Nagourney, MD, Peter Nygren, MD, PhD, Rob Pieters, MD, PhD, Peter Staib, MD, Ulf Tidefelt, MD, PhD, C. Michel Zwaan, MD, PhD and Larry M. Weisenthal, MD, PhD.

Abstract

Background: There has been a long history of Individualized Tumor Response (ITR) testing to aid drug selection in tailored therapy for leukemia and lymphoma. Almost all the published evidence suggests that the results produced provide useful prognostic information and added value that is independent of other patient variables. Trials have shown ITR test results correlate with subsequent patient response and survival. However, results have not been so readily accessible due, in part, to multiple descriptive terms.

Terminology: As a result, groups undertaking ITR with leukemias, lymphomas and solid tumors have agreed to use the term 'Individualized Tumor Response' to describe the effect of anticancer treatments on whole living tumor cells freshly removed from cancer patients. This term does not include tests with subcellular fractions, animals or cell lines.

Methods: All methods measure cell death: fresh tumor is removed from the patient, treated with an anticancer regimen in vitro for 2-7 days and tumor survival assessed. ITR testing for chemotherapy and radiotherapy has recently been extended to cover newer agents (Weisenthal, 2007).

Results: Multiple publications have shown assays correlate well with each other, allowing this meta-analysis. We found 1929 published ITR test results compared with patient response and analysed them to determine relative risk (Rel Risk) of clinical response after treatment with ITR-test-sensitive (ITR+) vs ITR-test-resistant (ITR-) regimens:

Comparison of Ex VTR test results with clinical response rate (RR) and relative risk (Rel Risk)

Diagnosis	#	Clinical RR	RR ITR+	RR ITR-	Rel Risk IVT+	Rel Risk IVT-
ALL	304	81.3	90.6	49.3	0.90**	1.65***
ANLL	621	72.0	87.9	35.8	0.82***	2.01***
CLL	720	69.0	82.5	18.8	0.83***	3.66***
NHL	85	54.1	72.9	11.5	0.74	4.69***
Other	199	61.3	78.2	8.3	0.78***	7.36***
Total	1929	70.4	84.6	28.3	0.83***	2.48***

*, 2P=0.25; **P=0.002; ***2P<0.0001; #, number of patients

Overall, the response rate for patients given ITR+ drugs (84.6%) is significantly greater than for patients treated with ITR- drugs (28.3%). The relative risk of not responding was significantly reduced by treatment with an IVT+ regimen (0.83; 95% Confidence Interval 0.80-0.86) but increases to 2.48 (2.15-2.87) when treated with an IVY- regimen. Published comparisons of ITR with patient survival have all shown better survival for patients treated with ITR+ drugs compared with patients treated with ITR- drugs. A randomized controlled clinical trial of the efficacy of ITR in CLL is ongoing.

Conclusions: Compared with newer methods being developed to prove tailored therapy (such as genomic analyses), IOTR testing provides a functional profile of how whole tumor cells respond to toxic insult. This is far closer to what happens in the patient than the measurement of the effect on genes or proteins. Further investment in ITR testing – technologies that produce clinically significant results for tailored therapy – is warranted.