Response-related Prognostic Factors: The Cytogenetic Response

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What is the role of cytogenetic monitoring in the era of quantitative RT-PCR?
Sensitivity of monitoring strategies

Leukemia cells

- Blood counts – 2%
- Cytogenetics – 14%
- PCR – 84%
- Undetectable range
Historical reminder
Cytogenetic response as a prognostic marker in patients treated with interferon-α
Survival of IFN-treated patients according to cytogenetic response at 24 months

Rosti et al, Semin Hematol 2003
Correlation between the incidence of major cytogenetic response and survival

Figure 1. MCgR rates reported from 12 studies of IFN alone (●) and four studies of IFN + LDAC (○) plotted vs 5-year survival. The relationship is significant ($r = 0.662$, $r^2 = 0.439$, $P = .005$).

Rosti et al, Semin Hematol 2003
Correlation between cytogenetics and qPCR

Ross et al., Leukemia 2005
Overall survival at 48 months – CML late CP

MCyR = CCyR + PCyR

Estimated rate at 48 months:
- CCyR at 3 months: n=52, 94.0%
- PCyR at 3 months: n=100, 93.9%
- No MCyR at 3 months: n=191, 76.5%
- Other: n=111, 76.9%

p<0.0001

Silver et al, ASH 2004
Risk of MCR loss according to time to MCR achievement

Months since MCyR

% without loss of MCyR

MCyR by <=3 mths
MCyR by >3 to <=6 mths
MCyR by >6 to <=12 mths
MCyR later than 12 mths

= Censored observations

Courtesy of Dr. B. Druker, Portland
Progression free survival according to cytogenetic response at 3 months

% without progression

Months since randomization

Courtesy of Dr. B. Druker, Portland
Progression free survival according to cytogenetic response at 6 months

Days since randomization

% without progression

36-95% Ph+

36-65% Ph+

<36% Ph+

CCyR

No CyR

Courtesy of Dr. B. Druker, Portland
Progression free survival according to cytogenetic response at 12 months

CyR at 12 months

% without progression

Months since randomization

Courtesy of Dr. B. Druker, Portland
Is there a role for FISH in monitoring response?

Conveniently done on peripheral blood but

- gain of sensitivity over conventional cytogenetics max. 1 log
- not validated in prospective trials
- misleading in individual cases

Reinhold et al, Leukemia 17(10):1925-9, 2003
PFS by time to CCR

% without PD

Time to CCyR

- - - - 3 months
- - - - >3-<=6 months
- - - - >6-<=12 months
- - - - >12 months

P = 0.278

Months since randomization

Courtesy of Dr. B. Druker, Portland
Conclusions

Early chronic phase

- Cytogenetic response at 6 months: first relevant cytogenetic prognosticator

- CCR at 12 months: accurately predicts freedom from progression to AP/BC in >95% of patients → cytogenetics preferable if reliable qPCR is unavailable

- CCR seems to override pretherapeutic Sokal risk