Impact of soluble TNF-Receptors (sTNF-Rs) shedding on outcome in patients treated with NGR-hTNF

Paolo Zucali1, Matteo Simonelli1, Fabio De Vincenzo1, Elena Lorenzi1, Armando Santoro1, Antonio Lambiase2, Claudio Bordignon2
1Department of Oncology, Humanitas Cancer Center, Rozzano, Italy; 2MolMed, Milan, Italy

Background and methods

- NGR-hTNF (asparagine-glycine-arginine human tumor necrosis factor) selectively damages CD13-overexpressing tumor vessels and displays a biphasic dose-response curve with activity shown at very low or high doses1
- TNF effects are mediated through its two receptors, TNF-R1 and TNF-R2, which also circulate in soluble forms upon shedding, thus competing with cell-surface receptors for free ligand2
- Shedding of TNF-R1, and especially TNF-R2, from membrane can lead to a desensitization of the cell to the TNF-mediated apoptotic signaling2
- The impact of this counterregulatory mechanism on NGR-hTNF activity was retrospectively assessed in two phase I trials (n=60; median age, 60 years; M/F 44/16; PS 0/1-2 25/35; median number of prior lines, 3)
- NGR-hTNF was given every 3 weeks at low (0.2 to 1.6 μg/m² n=14) or high doses (60 to 325 μg/m² n=46)4
- Tumor assessment by RECIST was done every 6 weeks until progressive disease (PD)
- Logistic and Cox regression models were used to test the associations between baseline-normalized plasma levels of sTNF-Rs after 1st cycle and clinical outcomes in terms of disease control rate (DCR), rate of patients without PD at 6 weeks), progression-free survival (PFS) and overall survival (OS)

Baseline-normalized sTNF-Rs levels after 1st cycle

Efficacy by sTNF-R1 levels after 1st cycle

OR=4.9
p=0.01

43%

sTNF-R1 ≤ 2.8* ng/mL (n=15)

sTNF-R1 > 2.8* ng/mL (n=45)

HR=0.41 p=0.001

25th percentile

Percentage of patients

DCR
3-month PFS rate
6-month PFS rate

13%
12%
0%

43%

29%

Duration of disease control by sTNF-R2 levels after 1st cycle

Overall results

- After first cycle, sTNF-Rs increased dose proportionally (p=0.0003) and sTNF-R2 peaked significantly higher than sTNF-R1
- Using the interquartile range as cut-off values, the levels of sTNF-Rs were grouped into low, intermediate or high, respectively
- Patients with low sTNF-Rs levels (25th percentile) had significantly improved efficacy outcomes (DCR and PFS)
- By multivariate analyses adjusted for age, sex, PS and prior lines, low sTNF-Rs levels remained independent predictor of higher DCR and longer PFS
- The highest sTNF-R2 levels (75th percentile) were associated with the worst OS rates

Conclusions

- NGR-hTNF induces dose-dependent shedding of sTNF-Rs that may block drug effects
- Patients with low post-dosing sTNF-Rs (or receiving low drug doses) had higher DCR and longer PFS than those with high post-dosing sTNF-Rs (or receiving high drug doses)
- Early changes in sTNF-Rs shedding may identify patients who have a greater likelihood of benefit from NGR-hTNF

References

4. Zucali PA et al. ASCO 2012; Abst 2580

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