ABSTRACT

Background: NGR-hTNF is a VTA expressing a tumor necrosis factor-α (TNF-α) that selectively binds to amphiregulin (NGR) expressed on tumour vascular endothelium. At low doses, NGR-hTNF combines activity on tumour vascular permeability and direct anticancer activity. Consequently, preliminary data indicate significant synergy between low doses of NGR-hTNF and cisplatin. Methods: PIIs with other solid tumors were treated with low doses (12-200 fold lower than MTD) of NGR-hTNF given as a doubling-dose scheme (0.2-0.4-0.8-1.6 µg/m²) at 1-hr intravenous infusion, in combination with cisplatin 80 mg/m² given as a 1-hr iv infusion every 3 weeks. A 3+3 escalation/de-escalation design was followed. Blood samples for PK analysis were collected after the first 3 cycles. Results: 19 pts (median age 59 years; range, 47-75); 14M/5F; ECOG PS 0-1 (10) in enrolled. Tumour was colon in 37% (6); breast in 22% (4); ovarian in 11% (2); melanoma in 11% (2); lung in 11% (2); renal in 11% (2); sarcoma in 11% (2); bladder in 2% (1); breast/melanoma in 2% (1). At 0.2 µg/m² (n=4), 0.4 µg/m² (n=3) and 0.8 µg/m² (n=4), with 9 and 8 pts pre-treated with platinum- and oxaliplatin-based regimens, respectively. Best responses were CR (n=2), PR (n=7), SD (n=7) and PD (n=3). NGR-hTNF PK was simple monoexponential with a half life of 24-42 h. The combination was safe without PK or DLT interaction or exacerbation of platinum-associated toxicity profile. As expected for the low doses NGR-hTNF Cmax and AUC increased linearly with dose. The combination was safe without PK interaction or exacerbation of platinum-associated toxicity profile. Figure 1: Cyclic NGR-hTNF peptide binds specifically to CD13/aminopeptidase N (APN) isoform selectively expressed by endothelial cells of newly formed human tumor vessels
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Pharmacokinetics

NGR-hTNF was found to have antitumour activity also at doses in the picogram range (equivalent to a dose of 0.3 µg/m² in humans) in preclinical model, without induction of circulating TNF receptors shedding (Figure 2).

Additionally, low doses of NGR-mTNF significantly increased the antitumour activity of cisplatin, with maximal synergism being observed with a 2-hour delay between NGR-hTNF and cisplatin administration (Figure 3).

Figure 1: Reconstituent fusion protein consisting of NGR peptide and human Tumour Necrosis Factor-alpha (TNF-α) (TNF-R1 and TNF-R2) ( vincristine (VCR))

Figure 2: Low doses of NGR-hTNF do not induce TNF-R2 shedding while triggering antitumour effects

Figure 3: Synergistic antitumour activity of NGR-mTNF with cisplatin

Figure 4: Study design, dose and assessment

Conclusions

In a phase I study evaluating a dose-distribution ranging from 0.2 to 60 µg/m² the MTD of NGR-hTNF was established at 45 µg/m² when given as single agent once every 3 weeks.

Conversely, a further phase I trial exploring the low-dose range of NGR-hTNF from 0.2 to 4 µg/m² selected the dose of 0.8 µg/m² as the optimal biological dose, based on dynamic imaging changes and preliminary antitumour activity.

Methods

Phase I trials

In a phase I study evaluating a dose-interval ranging from 0.2 to 60 µg/m² the MTD of NGR-hTNF was established at 45 µg/m² when given as single agent once every 3 weeks.

Conversely, a further phase I trial exploring the low-dose range of NGR-hTNF from 0.2 to 4 µg/m² selected the dose of 0.8 µg/m² as the optimal biological dose, based on dynamic imaging changes and preliminary antitumour activity.

Results

From July 2007 to April 2008, 22 patients resistant or refractory to standard treatments were enrolled.

Baseline characteristics were: Male/Female 14/8; ECOG PS 0/1 12/10; median age 60 years (range 47-75).

Trials of NGR-hTNF administered at low dose with cisplatin was safe without apparent PI interaction or exacerbation of platinum-associated toxicity.

As expected for using a low-dose range of NGR-hTNF, MTD was not reached.

Combination of NGR-hTNF 0.8 µg/m² with cisplatin 80 mg/m² showed promising preliminary antitumour activity also in platinum-pretreated patients and will be further developed in selected tumour types.

Acknowledgements

References

4. Gallo-Stampino C. et al. ASCO 2007; Abs 3540