Published in final edited form as:

J Immunother. 2003 ; 26(2): 179–180.

Continuous Intravenous Administration of Live Genetically Modified *Salmonella Typhimurium* in Patients With Metastatic Melanoma

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To the Editor:

In the January 1, 2002 issue of the *Journal of Clinical Oncology*, Toso et al. (1) published a phase I study on the intravenous administration of a bolus of attenuated *Salmonella typhimurium* to patients with metastatic melanoma treated at the National Cancer Institute. We now present an update of our findings in four additional patients who received a 4-hour infusion of live genetically modified *Salmonella typhimurium* (VNP 20009). As in the previous study, this bacteria had been genetically modified to alter its pathogenicity and to attempt to increase its localization to sites of growing cancer.

In the initial study, the maximum tolerated dose for a 30-minute infusion was 3×10^8 cfu/m²; yet, only one patient of three had a tumor biopsy culture positive for VNP20009 (1). With these findings, we decided to infuse the maximum tolerated dose over a 4-hour time period. The hypothesis was that maintaining high circulating levels of bacteria during the entire 4-hour infusion would increase the delivery of the VNP20009 to the tumor, thereby aiding in obtaining a high level of bacterial colonization ($>10^7$ cfu/g). In addition, the 4-hour infusion might be better tolerated than the shorter dosing interval.

Four patients were enrolled in this study. They had the same eligibility criteria as the initial cohort (1). The patients ranged in age from 40 to 56 years, and all had progressed through previous therapy. The 4-hour infusion was well tolerated. Side effects during the therapy were minor, including transient fever, chills, and emesis. One patient had a grade three transient episode of hypoxia requiring oxygenation via nasal cannula and migraine headaches resulting in delay of discharge from the hospital. Another patient had a grade three hypophosphatemia that resolved in 24 hours. In addition, he had a grade four hyperuricemia for which the patient had a known history before therapy.

Blood cultures were obtained at preset time intervals to determine the presence of VNP20009 in the bloodstream (Table 1). No patient had a positive blood culture beyond 6 hours from the start of infusion. Likewise, all patients had negative daily urine and stool cultures during their hospital stay, as well as at 2-week and 1-month follow-up (data not shown).

All four patients underwent excisional tumor biopsy within 2 weeks of therapy (Table 1). The first patient received a single dose of preoperative antibiotics, cefazolin, before her biopsy. Only one colony of *Salmonella* was found in the tumor specimens. At evaluation 1-month after

therapy, two patients had significant progression of disease and were treated with other therapy regimens. The third patient was rendered free of disease at the time of surgery and is currently disease free at 3 months after therapy. The fourth patient had an initial mixed response with decrease in size and number of some subcutaneous lesions but had progression of disease at 2-month follow-up and was moved to another treatment regimen.

In summary, *Salmonella* can be safely infused into humans with mild side effects over a 4-hour time period at a dose of 3×10^8 cfu/m². It was not possible to detect *Salmonella* in blood cultures beyond 6 hours from the start of infusion. *Salmonella* was not able to be cultured from biopsies performed at 2 weeks. No objective clinical responses were noted in any of the patients in this cohort.

REFERENCES

1. Toso JF, Gill VI, Hwu P, et al. Phase I study of the intravenous administration of attenuated salmonella typhimurium to patients with metastatic melanoma. J Clin Oncol 2002;20:142–152. [PubMed: 11773163]

TABLE 1
Blood cultures obtained at preset time intervals to determine the presence of VNP20009 in bloodstream

Time, hr	0	0.5	2	4	4.5	6	24	48	72	>72	Biopsy result [§]
Pt #1	- [*]	2+ [†]	2+	2+	-	1+ [‡]	-	-	-	-	1 Salmonella colony found in specimen (58cfu/g)
Pt #2	-	-	2+	2+	1+	-	-	-	-	-	Negative x2 tumor specimens
Pt #3	-	2+	2+	2+	1+	1+	-	-	-	-	Negative x2 tumor specimens
Pt #4	-	2+	2+	2+	1+	1+	-	-	-	-	Negative specimen

^{*} No salmonella detected.
[†] Salmonella detected in both aerobic and anaerobic bottles.
[‡] Salmonella detected in either aerobic or anaerobic bottle.
[§] Pt #1 biopsy performed 5 days after infusion; all other biopsies performed 14 days after infusion.