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# Session 3: Cancer – II

*Wednesday 8 October 2003. Moderators: Kohzoh Imai and Nils Lonberg*

[14.00–14.45]
[Keynote Lecture]
**Designing therapeutic human antibodies for the oncology clinic**
Mark C. Glassy
*RMRF Foundation, San Diego, USA*

Abstract not received.

[14.45–15.15]
**Biodistribution of an engineered antibody for radioimmunotherapy of adenocarcinomas**
Ruby Meredith[a], Andres Forero[a], Sui Shen[a], M.B. Khazaeli[a], Mark Carpenter[a], Jeff Schlom[b] and Albert LoBuglio[a]
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A genetically engineered molecule was constructed with CDR grafting from murine CC49 and deletion of the CH2domain. This was done to overcome problems of murine antibody immunogenicity and the prolonged plasma circulation of humanized reagents. CC49 is a high-affinity, second generation antibody against a pan-carcinoma antigen TAG-72 that is expressed on the majority of colorectal, gastric, breast, ovarian, prostate, pancreatic, and lung carcinomas. As the first clinical experience with HuCC49ΔCH2, patients with metastatic colon cancer have received IV administration of $^{131}$I-HuCC49ΔCH2. In the first 4 patients biodistribution/pharmacokinetics, dosimetry and immunogenicity were studied after a 10 mCi tracer dose (20 mg HuCC49ΔCH2). As expected the plasma half-life was short (20 $+/-$ 2.6 hours) compared to murineCC49 (50 hours) and the mean clearance rate significantly greater ($p < 0.001$). Table 1 shows the mean and standard deviation for pharmacokinetic parameter estimates resulting from a one-compartment bolus model. These were generated using the NLIN procedure in SAS.

The $^{131}$I-HuCC49ΔCH2 biodistribution was similar to that of murine CC49 with localization to known disease sites and the greatest normal organ activity in the liver and spleen. The mean and range for the whole body and marrow radiation dose estimates were 0.15 Gy/GBq (range 0.14–0.16) and 0.27 Gy/GBq (range 0.23–0.31), respectively. The whole body dose was well below $^{131}$I-murine CC49 (0.2 Gy/GBq) and for 3 tumors assessed, the tumor:marrow ratio was 7.4. Based on these initial favorable results, dose escalation was initiated. Six patients have been treated with a single infusion of 75 mCi/m$^2$ $^{131}$I-HuCC49ΔCH2. One patient developed a modest antibody response to HuCC49ΔCH2 within 6 weeks.

[15.15–15.45]
**Immune responses in breast cancer patients immunized with an anti-idiotype antibody mimicking NeuGc-containing gangliosides**
Alain Díaz[a], Mauro Alfonso[a], Ruby Alonso[a], Gisselle Saurez[a], Mayelín Troche[a], Mauricio Catalá[b], Rosa María Díaz[a], Rolando Pérez[a] and Ana María Vázquez
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A phase I clinical trial was conducted in patients with stage III/IV breast carcinoma who were treated with the anti-idiotype mAb 1E10 specific to an Ab1 mAb able to react specifically with N-glycolyl-containing gangliosides and with antigens expressed on human melanoma and breast carcinoma cells. Patients were treated with 1 or 2 mg of aluminum hydroxide-precipitated 1E10 mAb, every other week for six injections. Two patients of each dose were reimmunized 7–9 months after finished the induction phase. There were not differences between the two levels of dose tested in relation to toxicity and immunogenicity. No evidences of serious or unexpected effects were observed. In hyperimmune

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Table 1
Pharmacokinetics of $^{131}$I-HuCC49$\Delta$CH2

| Pt. | $C_{max}$ ($\mu$Ci/ml) | $T_{1/2}$ (h) | MRT (h) | AUC (h/$\mu$Ci/ml) | Cl (ml/h/Kg) | $V_D$ (ml/Kg) | $R^2$ |
|---|---|---|---|---|---|---|---|
| 1 | 4.1 | 20 | 29 | 12 | 1.5 | 45 | 0.977 |
| 2 | 3.4 | 24 | 35 | 11 | 1.4 | 50 | 0.991 |
| 3 | 3.0 | 19 | 28 | 9 | 1.5 | 42 | 0.996 |
| 4 | 3.5 | 18 | 26 | 8 | 1.4 | 35 | 0.986 |
| Mean | 3.5 | 20 | 29 | 10 | 1.5 | 43 | 0.988 |
| Std Err | 0.5 | 2.6 | 4 | 2 | 0.1 | 6 | N/A |

$C_{max}$ = peak concentration; $T_{1/2}$ = serum half-life; MRT = median residence time; AUC = area under the curve; Cl = clearance; $V_D$ = volume of distribution normalized by patient weight; $R^2$ = correlation coefficient.

sera from eight of the nine patients who received at least four doses of anti-Id vaccine preparations, strong specific responses were observed both against 1E10 mAb and NeuGc-GM3 ganglioside (Ab3 Id+Ag+). These results showed an "internal image" behavior for 1E10 Ab2 mAb in humans, in contrast with our previous results obtained in mice, rabbit and monkeys. Strikingly, Ab1′ antibodies able to bind to NeuGc-containing gangliosides, but not to 1E10 mAb (Id-Ag+) were detected in immunized patients' sera.