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Short Research Article

177Lu-DOTA-Tyr3-TATE radiotherapy experiments using animal models. Flow cytometric analysis in evaluation of therapeutic effect†

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Introduction

DOTA-Tyr3-TATE (1,4,7,10-tetraazacyclododecane-*N*,*N*′,*N*″,*N*‴-tetraacetic acid tyrosine 3-octreotate), a bioconjugate of a somatostatin analog was labeled with ^{177}Lu (specific activity 45 Ci/mg) in 0.4 M acetate buffer pH 4.5.[1–3] After 30 min incubation at 80°C ^{177}Lu-DOTA-TATE with radiochemical purity higher than 95% and specific activity 1.2 Ci/μM was obtained and used for comparative evaluation of peptide receptor radionuclide therapy in single and multiple therapeutic doses.[4,5] HRS1 (a hepato-colangiom carcinoma), bearing

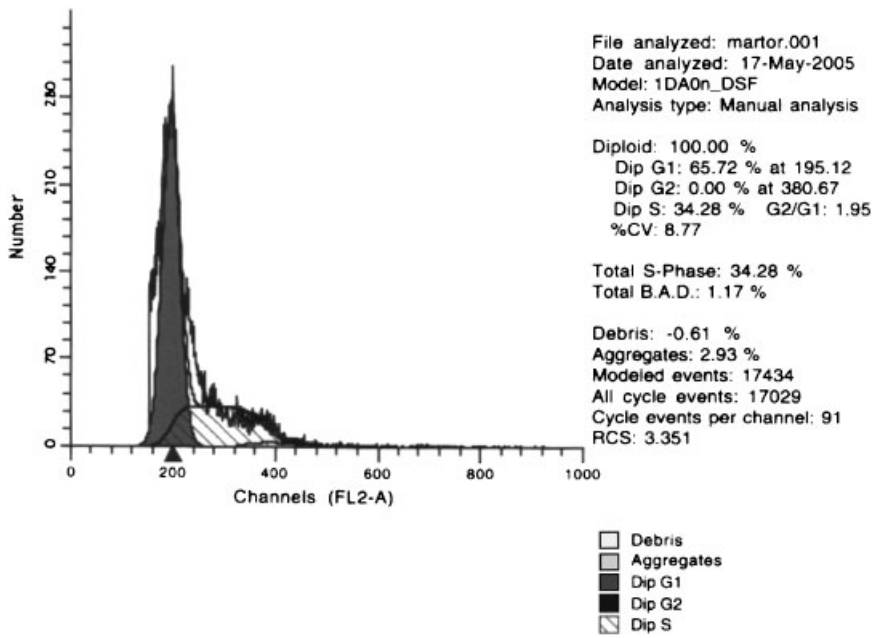

Figure 1 Flow-cytometric DNA content on the HRS1 tumor (control).

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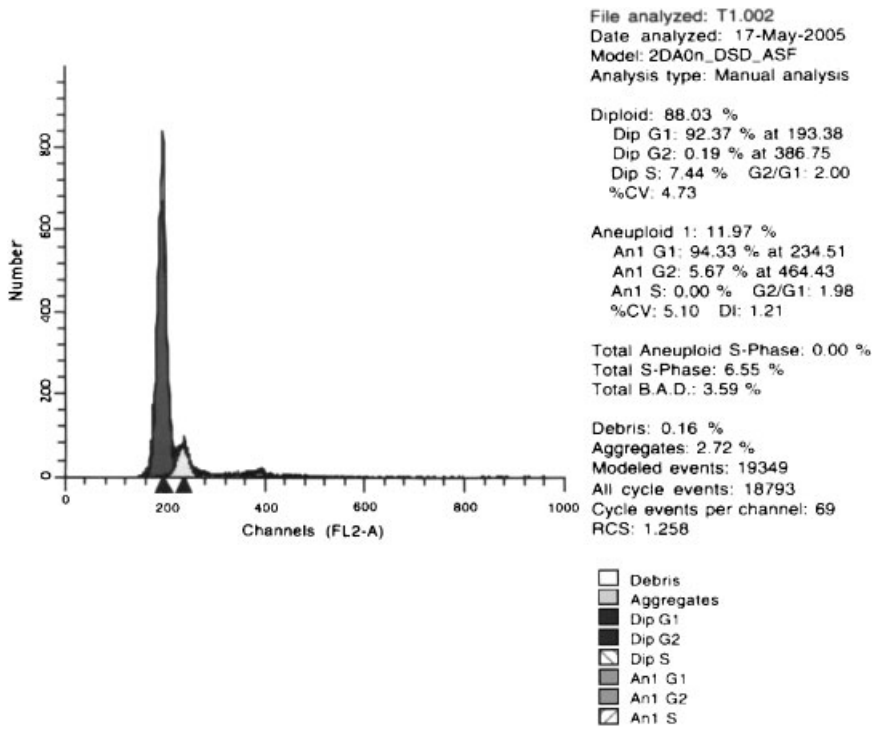

Figure 2 Flow-cytometric DNA content on the HRS1 tumor (RSD).

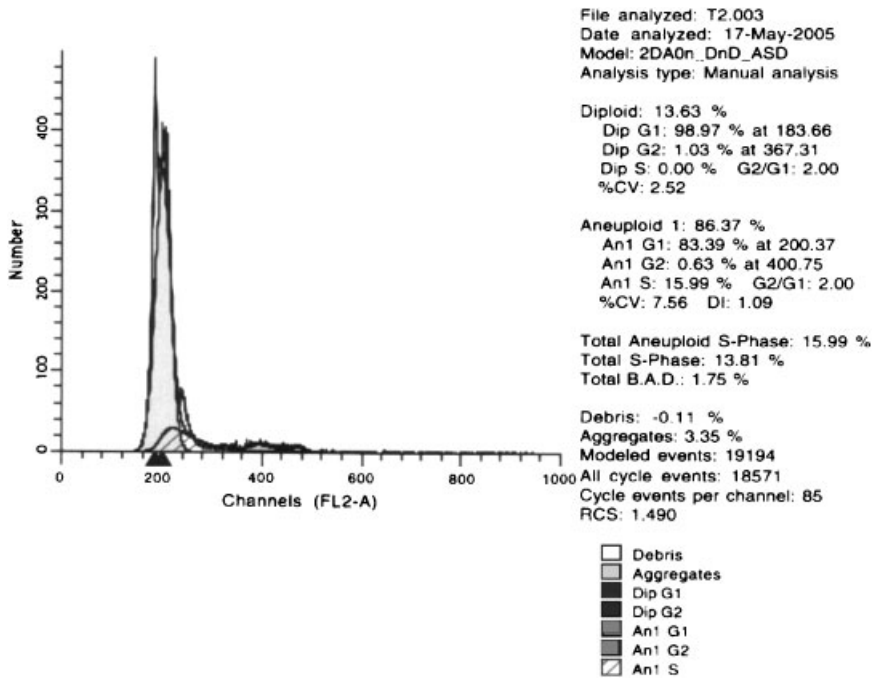

Figure 3 Flow-cytometric DNA content on the HRS1 tumor (RMD).

Lewis rats prepared 10 days prior to radiobiologic studies were treated with 15 mCi ^{177}Lu- DOTA-Tyr3-TATE by i.v. administration in single and multiple doses.

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Table 1 Effects of ^{177}Lu-DOTA-Tyr3-TATE radiotherapy on the HRS1 tumor

Sample	P1						P2							P1/P2 (%)
	G_0/G_1 (%)	S (%)	G_2+M (%)	PI (%)	G_2/G_1	CV	G_0/G_1 (%)	S (%)	G_2+M (%)	PI (%)	G_2/G_1	CV	DI	
Control	—	—	—	—	—	—	65.72	34.28	0.00	34.28	1.95	8.77	—	—/100
RMD	92.37	7.44	0.19	7.63	2.00	4.73	94.33	0.00	5.67	5.67	1.98	5.10	1.21	88.03/11.97
RSD	98.97	0.00	1.03	1.03	2.00	2.52	83.39	15.99	0.63	16.62	2.00	7.56	1.09	13.63/86.37

Results and discussion

After therapy, the tumor samples were processed and analyzed by flow-cytometric methods for DNA content estimation in the cell cycle by the following parameters: G_0, G_1, G_0/G_1 phases, representing diploid DNA content, G_2+M phase, cells with tetraploid DNA content and S phase, tetraploid and diploid DNA content. Other parameters are DNA index, proliferation index (PI=S+ G_2+M), G_2/G_1 phase ratios and coefficient of variation (CV). The DNA histograms of the analyzed samples are presented in Figures 1, 2 and 3. Figures 2 and 3 show the presence of two cell populations: normal cell population (diploid) – P1 and tumor cell population (aneuploid) – P2 in partial overlap.

The results obtained from DNA histograms (Table 1) show that the HRS1 tumors are very aggressive (S = 34.28%, PI = 34.28%).

After therapy S and PI values are decreasing as a result of therapeutic approach: S = 15.99%, PI = 16.62% and DI = 1.21 for single dose treatment, respectively, S = 0%, PI = 5.67% and DI = 1.09 for multiple doses therapy. The results countenance the treatment of sstr positive tumors with ^{177}Lu- DOTA-Tyr3-TATE by multiple dose therapy.

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