High-dose gallium-67 therapy in patients with relapsed acute leukaemia: a feasibility study

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Summary Gallium-67 (67Ga) accumulates in malignant tissues via the transferrin receptor without need for a monoclonal antibody and emits cytotoxic low-energy electrons. In this study we investigated the feasibility, pharmacokinetics, toxicity and preliminary efficiency of high-dose 67Ga injected intravenously (i.v.) in patients with acute leukaemia not responding to conventional therapy. Twelve doses of 36–105 mCi of Gallium67 citrate were administered as a push injection to eight patients with resistant leukaemia in a pilot study. All five patients with acute myeloid leukaemia (AML) and three patients with acute lymphoblastic leukaemia (ALL) had resistant disease or resistant relapse. No (sub)acute toxicity was observed. Independent of the administered dose, whole-blood radioactivity levels 10 min after administration measured only 1.25 ± 1.39 pCi ml−1, indicating a large volume of distribution. Urine excretion in the first 24 h ranged from 18% to 51.5% (median 29.5%) of the administered dose. Cellular uptake of 67Ga was less than in previous in vitro studies. Whole-body radiation dose was estimated to be 0.25 ± 0.03 cGy mCi−1. Red marrow dose was estimated to be between 0.18 ± 0.02 and 0.97 ± 0.12 cGy mCi−1. One definite response was observed in an ALL patient with disappearance of skin lesions, normalisation of the enlarged spleen and profound leucopenia. Three other patients showed transient reductions in white blood cell counts without disappearance of blasts from the peripheral blood. We conclude that high-dose i.v. 67Ga can be safely administered but that the uptake of 67Ga in blast cells must increase to make 67Ga therapeutically useful in patients with relapsed leukaemia.

Keywords: Gallium-67; cytotoxicity; acute leukaemia; radionuclide therapy; radiotherapy

Although the initial remission rate of acute leukaemia in adults is high (70–80%), a considerable portion of patients eventually die of their disease (Rohtatier et al., 1990). Therefore, new treatment modalities have to be explored. The idea of therapy with a radionuclide that accumulates in the target tumour cell by itself is appealing. Recently, promising results were reported from radioimmunotherapy with a 131I-labelled anti-CD33 monoclonal antibody (MAB) in patients with relapsed or refractory myeloid leukaemia (AML) (Appelbaum et al., 1990; Schwartz et al., 1993). However, problems related to MAB-mediated radiotherapy include adverse reactions caused by the administration of foreign protein and the forming of human anti-mouse antibodies (HAMA), precluding repeated cycles of therapy (Rosen and Kuzel, 1993).

We are currently investigating the therapeutic potential of the radionuclide gallium-67 (67Ga), which accumulates in malignant tissues via the transferrin receptor (Nelson et al., 1972; Anghieri et al., 1977; Chitambare et al., 1986; Leeuwen-Stok et al., 1993). We have shown that 67Ga is cytotoxic in vitro to human HL60 myeloid cells and U937 and U715 lymphoid cells (Jonkhoff et al., 1993, 1994; Leeuwen-Stok et al., 1993). However, the relative biological effectiveness (RBE) of 67Ga was approximately 1.0, indicating a rather low effectiveness for cell kill of its low-energy electron emissions, which confirmed earlier studies (Hofer et al., 1975; Jonkhoff et al., 1994). Radionuclides mentioned as candidates for radionuclide therapy are generally beta-emitting nuclides including yttrium-90, iodine-131, rubidium-86, phosphorus-32, indium-114m, samarium-153 (Coursey et al., 1991; Rao and Howell, 1993). Auger electron emitters, such as 125I[II]jUDR have favourable properties, but are considered too toxic for in vivo use (Makrigiorgos et al., 1990). The reason 67Ga was never considered for therapy might be because of insufficient data on its effectiveness, its low-energy electron emissions, precise intracellular localisation and heterogeneous uptake. In vitro blast cells of some AML patients accumulate 67Ga strongly, and after incubation with 80 μCi ml−1 67Ga, clonogenic survival was reduced more than 90% compared with control cells. In some blast cells clonogenic growth was completely abolished after only 20 μCi ml−1 67Ga (Jonkhoff et al., 1995). Some of the relative ineffectiveness of 67Ga for cell kill might be compensated by a high in vivo cellular uptake of 67Ga and favourable pharmacokinetic data.

In this study we report the first in vivo data concerning toxicity and pharmacokinetics and preliminary efficacy of 67Ga in eight patients with resistant acute leukaemia.

Materials and methods

Patients

Patients with end stage acute leukaemia were entered into the study after giving informed consent according to the Declaration of Helsinki. The study was approved by the ethical committee of the Free University. Five patients with acute myelogenous leukaemia (AML) and three patients with acute lymphoblastic leukaemia (ALL) were included. All patients had a WHO performance status of 0 or 1. No patient had pre-existent cardiac, pulmonary or renal disease. Supportive care medication in most patients included ciprofloxacine, flucanazol, ranitidine, tranexamic acid, and transfusion of blood products. The only cytostatic co-medication allowed was prednisone or dexamethasone in ALL and hydroxyurea in AML patients, in order to control peripheral blast counts.

67Ga

Carrier-free 67Ga was obtained from Mallinkrodt Diagnostics (Petten, The Netherlands) as 67Ga chloride. 67Ga citrate for intravenous injection, with a low citrate concentration, was prepared as described previously (Jonkhoff et al., 1993). 67Ga citrate was given in a volume of 10 ml as a rapid intravenous push, except in patient 5 who was given a second injection of 5 mCi as a 1 h infusion in order to study urinary excretion and transferrin binding. Radiation safety precautions, including rules for hospitalisation on a nuclear medicine unit, were in accordance with accepted guidelines (National Council on Radiation Protection, 1970).
The lowest dose level was based on experience in lymphoma patients, who suffered no side-effects other than myelosuppression after administration of 40–60 mCi $^{67}$Ga i.v. (Huijgens et al., 1993). Before and biweekly after $^{67}$Ga administration, whole blood cell counts were determined. Liver enzymes and renal function were tested weekly.

**Transferrin receptor**

The percentage of transferrin receptor-positive leukaemia blasts (5000 events) were analysed on a FACScan flow cytometer (Becton Dickinson). A FITC-conjugated mouse anti-human monoclonal antibody was used (Dako-CD71, Ber-T9; Glostrup, Denmark). An irrelevant IgG1 was used as isotype control.

**Cellular uptake of $^{67}$Ga**

Whole blood samples were drawn from the patient by venipuncture 10 min, 60 min and 24 h after $^{67}$Ga administration and put on ice immediately. After lysing erythrocytes using three drops of lysing solution the cellular $^{67}$Ga uptake and cellular $^{67}$Ga content was determined as described previously (Jorkhoff et al., 1995). All radioactivity values were corrected for physical decay (at $t = 0$).

**Pharmacokinetics**

Radioactivity of whole blood samples was measured 10 min, 60 min and 24 h after injection of $^{67}$Ga. The first 24 h after injection the urine was collected to measure the renal excretion of $^{67}$Ga. In one patient plasma samples on more time points were measured. In this patient (patient 8) the area under the curve (AUC) of $^{67}$Ga was analysed by Topfit 2.0, using a non-compartmental model (Tanswell et al., 1993).

**Scintigraphy**

Twenty-four hours after $^{67}$Ga administration a whole body scintigram was performed with a dual-head gamma camera and medium-energy collimators (ADAC Laboratories, Milpitas, CA, USA).

**Dosimetry**

In six patients (seven complete measurements) the blood and whole body data were used for red marrow dose calculations. The residence times of $^{67}$Ga in the blood and whole body were derived from numerical integration of the blood and urinary time activity curves. After 24 h we assumed no biological clearance and only physical decay of $^{67}$Ga.

With approach A the activity in the whole body was assumed to be homogeneously distributed (Plaizier et al., 1994a,b). With approach B the activity in the whole body was assumed to be equally divided between the remainder of the body and the skeleton. The latter approach was used to illustrate the theoretical 'maximal' effect of specific bone uptake on the red marrow dose.

The activity in the red marrow and blood was assumed to be equal (Siegel et al., 1990). Specific uptake in the red marrow is neglected because of lack of information on red marrow kinetics. Whole-body radiation dose was estimated from the whole body residence time.

Whole body and red marrow dose were calculated according to MIRDPOSE2 (Watson and Stabin, 1984). The kinetic and dosimetric data were compared with the ICRP-53 (International Commission on Radiation Protection, 1987) and MIRDPOSE2 standard.

**Statistics**

Statistical analysis was performed with Stat-Graphics 2.6 statistical computer program.

**Results**

**Toxicity**

Patient characteristics are presented in Table I. All patients had resistant or relapsed disease, and there were no curative options left. Serum transferrin and ferritin levels were $1.83 \pm 0.19\,\text{g}\,\text{L}^{-1}$ (range 1.59–2.04) and $5269 \pm 3783\,\text{µg}\,\text{L}^{-1}$ (range 2060–12444) respectively.

In total, 12 doses of $^{67}$Ga were delivered i.v. Doses ranged from 36–105 mCi. None of the patients was admitted for more than 24 h. No acute toxicity was observed. Two patients noted a slight fruity flavour. One patient noted increased bleeding tendency and muscle pains in the 4 days following 60 mCi $^{67}$Ga. However, no objective increase in bleeding tendency was observed and muscle pains did not occur after a second administration of 60 mCi $^{67}$Ga in the same patient.

No change in kidney or liver function was observed. Levels of lactate dehydrogenase (LDH) varied with disease activity, and were not correlated with $^{67}$Ga administration. Haematological effects were restricted to those on blast counts.

**Pharmacokinetics**

Table II shows the pharmacokinetics after 10 min. Most patients had whole blood levels between 1.0 and 1.5 µCi

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**Table I**

| Patient no. | Age | M/F | Diagnosis | CD71 (%) | Previous treatment | Status |
|-------------|-----|-----|-----------|----------|--------------------|--------|
| 1           | 27  | F   | AMLxM2    |          | a,b,c,ABMT,d       | Second relapse |
| 2           | 45  | F   | AMLxM1    | 23       | a,b,c,ABMT         | Second relapse |
| 3           | 62  | F   | AMLxM1    | 18       | a(2×),c(2×),b      | Resistant relapse |
| 4           | 58  | F   | AMLxM4    | 43       | a,b,c, + cyclosporin A | Resistant disease |
| 5           | 60  | F   | AMLxM5b   | 79       | a(2×),c            | Resistant relapse |
| 6           | 22  | M   | ALL       |          | c,e,b,d            | Resistant disease |
| 7           | 32  | F   | ALL       | 68       | e,f,g,h            | Second relapse* |
| 8           | 50  | M   | ALL       | 28       | e,f,ABMT           | First relapse |

Treatments: a, daunorubicin/ARA-C; b, amascanic/ARA-C; c, mitoxantrone/VP16 (etoposide); d, VP16 (3000 mg m$^{-2}$) + melphalan (100 mg m$^{-2}$); e, daunorubicin/vincristine/ asparaginase/prednisone; f, 6-mercaptopurine/methotrexate/ARA-C/ cyclophosphamide; g, vincristine/doxorubicin/dexamethasone; h, ARA-C/VP16. ABMT, autologous bone marrow transplantation busulphan 16 mg kg$^{-1}$ + cyclophosphamide. *Systemic + leptomeningeal relapse.
ml\(^{-1}\), with two patients (5 and 6) reaching higher levels of 4.5 \(\mu\)Ci ml\(^{-1}\). One h post injection (p.i.) blood levels were approximately halved, compared with 10 min p.i. The 24 h blood levels were approximately 30% of the 1 h blood levels.

One patient (patient 8) was more extensively monitored for plasma levels (Figure 1). A steep decrease in plasma radioactivity level was noted in the first minutes after administration. Pharmacokinetic data calculated in this patient are given in the legend of Figure 1.

Of the 12 administrations of \(^{67}\)Ga, urinary excretion was measured on nine occasions. The median urinary excretion of \(^{67}\)Ga in the first 24 h p.i. was 29.5% (range 18–51%) of the administered dose. In three patients the first 0–6 h urine portion was collected separately. These collections contained 22.1 mCi (27% of injected dose) in patient 4, 32.8 mCi (39.6% of injected dose) in patient 6 and 17.5 mCi (16.6% of injected dose) in patient 8.

**Cellular uptake and dosimetry**

Cellular uptake values of 11 \(^{67}\)Ga administrations were 1.57 ± 2.67% (range 0.07–9.00%), 1.57 ± 2.71% (range 0.05–8.70%) and 1.86 ± 2.00% (range 0.05–5.18%), 10 min, 60 min and 24 h after injection respectively (median value ± s.d.).

Cellular \(^{67}\)Ga content values of 11 \(^{67}\)Ga administrations were 1.73 ± 19.40 (range 0.08–66.22) \(10^{-3}\) pCi per cell, 0.89 ± 4.97 (range 0.04–17.15) \(10^{-3}\) pCi cell\(^{-1}\) and 0.27 ± 1.25 (range 0.02–3.41) \(10^{-3}\) pCi per cell, 10 min, 60 min and 24 h after injection respectively (median value ± s.d.).

The whole-body residence time was estimated to be 90.89 ± 12.40 h compared with 88.56 h calculated according to ICRP-53. We calculated a red marrow residence time of 0.41 ± 0.16 h, which differed considerably from the comparable ICRP-53 value of 4.78 h.

The whole body dose was estimated to be 0.25 ± 0.03 cGy mCi\(^{-1}\), which compares well with MIRD/ICRP-53 calculations of 0.24 cGy mCi\(^{-1}\). The red marrow dose depended on whether a homogeneous distribution was expected; approach A, 0.18 ± 0.02 cGy mCi\(^{-1}\) or 50% accumulation of the total activity in the skeleton was assumed; approach B, 0.97 ± 0.12 cGy mCi\(^{-1}\). The comparable MIRD/ICRP-53 value for the red marrow dose was 0.70 cGy mCi\(^{-1}\).

**Scintigraphy**

Figure 2a shows a 5 mCi diagnostic \(^{67}\)Ga scan without abnormalities; Figure 2b shows a \(^{67}\)Ga scan in a non-Hodgkin's lymphoma patient after high-dose gallium-67 citrate administration; and Figure 2c shows a similar scan in patient 8. The figure shows a representative image of a scintigraphy study in a leukaemia patient 24 h after a therapeutic dose of 105 mCi of \(^{67}\)Ga (patient 8). The marked increase of \(^{67}\)Ga accumulation in the skeleton is notable. Decreased activity is seen in the liver, and there is almost complete absence of bowel excretion.
**Response**

Objective judgement of response was hindered by the concomitant anti-leukaemic medication (hydroxyurea or corticosteroid). In Figure 3 white blood cell counts (WBC) in all patients are presented in relation to the medication. AML patients 3 and 5 showed a reduction in WBC following administration of $^{67}$Ga. Normal WBC values were only reached in patient 5, although the white blood cell differentiation still showed the presence of 52% blast cells. Furthermore, notable in this patient was the normalisation of the serum LDH from 1119 U l$^{-1}$ (N = 250 U l$^{-1}$) to 155 U l$^{-1}$. The response, however, was short-lived as the WBC increased 15 days after the second administration.

Of the ALL patients, patient 6 had a definite response with WBC decreasing $<0.1 \times 10^9$ l$^{-1}$, 20 days p.i., normalisation of the enlarged spleen, which ranged 7 cm beneath the left costal margin and disappearance of skin lesions. Patient 8 had an initial rise in WBC up to $200 \times 10^9$ l$^{-1}$ in 4 days. Dexamethasone was started followed by a steep decrease in WBC. However, it is unlikely that dexamethasone caused the ensuing leucopenia, which was probably an effect of the $^{67}$Ga administration.

![Figure 3](image-url)  
**Figure 3** Course of white blood cell counts in all patients during a varying observation period. The administration of high dose gallium-67 citrate is indicated. Concomitant medication and its dose is given. In patient 5 the platelet counts are indicated as well (dotted line).
In the present study eight patients with relapsed and/or resistant acute leukaemia received in total 12 doses of high-dose $^{67}$Ga. No acute side-effects were observed nor any extra-haematological effect. Myelotoxicity is considered to be the major and dose-limiting toxicity in most radionuclide therapies in lymphoma patients (Kaminski et al., 1993; Press et al., 1993). In our study myelotoxicity was apparent by the (transient) effect on blast cells but not in changes in erythrocyte and platelet requirements.

Whole blood levels of radioactivity were unexpectedly low, with values in six patients between 0.80 and 1.86 nCi ml$^{-1}$ 10 min after administration. We expected higher levels as $^{67}$Ga is temporarily confined to the plasma compartment by phagocytosis of transferrin (Vallabhajosula et al., 1980). For instance, in patient 8, with an estimated blood volume of 7.51 and who received 105 mCi, one would have expected an initial blood level of 14 nCi ml$^{-1}$ instead of the 0.80 nCi ml$^{-1}$ we found. Low plasma $^{67}$Ga levels are described following chemotherapy (Shepton and Martin, 1980) but this was not the case in patient 8. The observed steep initial decrease in plasma or blood $^{67}$Ga levels seem to disagree with pharmacokinetic data of $^{67}$Ga that describes a short-lived and a long-lived component with a biological half-life of approximately 30 h and 613 ± 83 h respectively (Cloutier et al., 1988). The urine excretion was unexpectedly high with a median value of 29.5% (range 18–51.5%) of the injected dose excreted in the first 24 h. The urinary excretion seems larger than the 26% of the injected dose of $^{67}$Ga in the first 7 days after injection that Nelson et al. (1972) observed in 23 patients.

Pharmacokinetic data of non-radioactive gallium nitrate report 24 h urinary excretion of 15–72% after a bolus injection (Hall et al., 1979; Kelsen et al., 1980). No difference in urinary excretion between bolus injection or 1 h infusion was observed in patient 5, who served as her own control. The observed pharmacokinetic differences could be related to the concomitant medication or differences in patient group. The iron status of our patients, who received frequent blood transfusions, could have been of influence. Another possibility is that our low-citrate formula of $^{67}$Ga influenced our data, as gallium-67 citrate can form multinuclear polymeric forms, gallium hydroxides or bind to serum proteins other than transferrin (Larson et al., 1978). We tried to measure the portion of $^{67}$Ga-Trf in the plasma samples by high-performance liquid chromatography (HPLC), but could not validate sufficiently the stability of the $^{67}$Ga-Trf binding during the procedure, as free gallium-67 citrate complexes with the silica of the column.

The uptake of $^{67}$Ga in the blast cells was approximately 40 times less than in our in vitro experiments (Jonkhoff et al., 1993, 1995; Leeuwen-Stok et al., 1993). This rather low cellular $^{67}$Ga uptake might be explained by insufficient Trf-receptor expression on blast cells, the relatively high Trf concentration in the blood/bone marrow compartment, which inhibits the uptake of $^{67}$Ga in the cell (Leeuwen-Stok et al., 1993) or the low blood levels of $^{67}$Ga. No apparent correlation was found between Trf receptor (CD71) expression, or $^{67}$Ga uptake in blast cells and in vivo response.

Our dosimetric calculations show similar whole body retention times between this study and ICRP-53. The seeming contradiction between a larger than expected urinary excretion and similar residence times to ICRP values can be explained by the neglect in our study of biological clearance after 24 h. The calculated activity in red marrow however is considerably lower than the red marrow activity suggested by the ICRP-53. The red marrow absorbed dose based on the ICRP-53 lies between red marrow absorbed dose calculations with assumed different skeleton activities (approach A or B). For individual patients the total red marrow dose varied between 10–17 Gy (approach A) and 52–110 Gy (approach B) depending on the chosen approach (data not shown). As we observed at least one definite clinical response, approach B seems more realistic. It is also possible that the absorbed whole body and red marrow doses are underestimated because microdosimetry was not taken into account (Van Dieren, 1993). Furthermore, we cannot exclude the possibility that bone marrow blast cells had a higher uptake of $^{67}$Ga than the peripheral blasts, as the minimal $^{67}$Ga content in the cells with only a few disintegrations in a million cells is not likely to result in the observed clinical response.

The body distribution measured by scintigraphy showed an abnormal pattern, compared with high-dose $^{67}$Ga administration in lymphoma patients (Huijgens et al., 1993). The skeleton was imaged more clearly and liver, spleen and bowel less intensively. We cannot exclude the possibility that the distribution in the skeleton is caused by the bone-seeking properties of $^{67}$Ga (Ando et al., 1989) or uptake in bone marrow blasts. More likely, however, the distribution in the skeleton is due to additional factors such as iron overload. Engelstad et al. (1982) described a similar $^{67}$Ga distribution in patients with multiple red cell transfusions.

Responses are difficult to interpret with concomitant anti-leukaemic medication. Two AML patients seemed to respond with decreasing WBC after $^{67}$Ga administration (patients 3 and 5), but these responses seem to be short lived. Blast cells remained in peripheral blood smears. Of the ALL patients, one had a definite response with disappearance of skin lesions and normalisation of the enlarged spleen. Profound leucopenia (WBC < 0.1 x 10$^{11}$\ liter$^{-1}$) was encountered from 15 days p.i. onwards, until death 2 months later. Another ALL patient (patient 8) had a very steep decrease in WBC, with disappearance of blast cells, following dexamethasone medication. This decrease in WBC might be caused by the $^{67}$Ga administration, as radionuclide therapy is known to exert its effect only after several days. In total, we observed one definite response (13%) and three possible responses (38%) out of eight patients.

Our conclusion is that high-dose $^{67}$Ga therapy is well tolerated, but cellular $^{67}$Ga uptake is relatively low. Pharmacokinetic data suggest a large proportion of non-transferrin-bound $^{67}$Ga, influencing urine excretion, body distribution and possibly cellular uptake. Nevertheless, transient responses and one definite response were noted. Therefore, we feel that if cellular $^{67}$Ga uptake can be enhanced by additional measures, such as desferrioxamine or iron-dextran administration (Shani et al., 1986), high-dose $^{67}$Ga therapy might be useful in leukaemia patients.

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