

Gallium in cancer treatment

Philippe Collery ^a, Bernhard Keppler ^b, Claudie Madoulet ^c, Bernard Desoize ^{c,*}

^a *Service de Cancérologie, Polyclinique Maymard, rue Marcel Paul, 20200 Bastia, France*

^b *Institute of Anorganic Chemistry, University of Vienna, Währinger strasse 42, 1090 Vienna, Austria*

^c *Laboratoire de Biochimie, EA 3306, Faculté de Pharmacie, IFR 53, 51 rue Cognacq-Jay, 51096 Reims Cedex, France*

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* Corresponding author. Tel.: + 33-03-26913731; fax: + 33-03-26913730.

E-mail address: bernard.desoize@univ-reims.fr (B. Desoize).

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Abstract

Gallium (Ga) is the second metal ion, after platinum, to be used in cancer treatment. Its activities are numerous and various. It modifies three-dimensional structure of DNA and inhibits its synthesis, modulates protein synthesis, inhibits the activity of a number of enzymes, such as ATPases, DNA polymerases, ribonucleotide reductase and tyrosine-specific protein phosphatase. Ga alters plasma membrane permeability and mitochondrial functions. Ga salts are taken up more efficiently and more specifically by tumour cells when orally administered. New compounds have been prepared: Ga maltolate, doxorubicin–Ga–transferrin conjugate and Tris(8-quinolinolato)Ga(III), which show interesting activities. Ga toxicity is well documented in vitro and in vivo in animals. In humans, the oral administration Ga is less toxic, and allows a chronic treatment, allowing an improvement of its bioavailability in tumours, by comparison with the parenteral use. The anticancer activity of Ga salts has been demonstrated but other effects have also been noted such as many bone effects that could be useful in bone metastatic patients. Its has also been shown that a long period of administration could induce tumour fibrosis. Ga is synergistic with other anticancer drugs. Although not as potent as platinum in vitro, the anticancer activity of Ga should not be ignored, but the schedule of administration still needs to be optimised and new compounds are now under clinical investigations. © 2002 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

Gallium (Ga) was discovered in 1875 by the French P.É. Lecoq de Boisbaudran, who observed that it had the predicted properties of ‘eka-aluminum’, the existence of which was predicted by Mendeleev 6 years earlier. Thus it was the first of Mendeleev’s elements to be uncovered. This discovery paved the way for the general acceptance of the periodic table.

It is a metal of main Group IIIa of the periodic table, with contains aluminium, indium and thallium. Its atomic number is 31, atomic weight 69.72 and melting point 29.78 °C. In most of its compounds Ga has an oxidation state of +3. The chemical behaviour of Ga is close to that of Fe⁺⁺⁺, in terms of its electric charge, ion diameter, coordination number and its electronic configuration [1]. Radioactive Ga 67 and Ga 68 show some promise in the study of bone cancer; as compounds of these isotopes are absorbed by the cancer deposits in the bone [2]. Anticancer properties were described for the first time in 1971 by Hart et al. [3,4].

2. In vitro studies

2.1. Change in DNA three-dimensional structure and synthesis

Tajmir-Riahi et al. [5] studied the interactions of

trivalent Ga with calf–thymus DNA in aqueous solution at different pH by infra-red spectroscopy, with Fourier transformation (FTIR). The most important interactions were observed from pH 4–5.

For a low Ga concentration (Ga⁺⁺⁺/DNA ratio = 1/80) Ga atoms were bound to DNA phosphate, forming a stable complex, but no interaction was noticed between the metal and nucleic bases. At higher Ga concentrations (ratio = 1/40) bonds appeared between Ga and nucleic bases and in this new complex the DNA helix was destabilized. When the ratio was > 1/40, major structural modifications appeared: for ratio > 1/20, strong interactions were observed between the metal and adenine or guanine, and for ratio > 1/10, interactions appeared with cytosine or thymine. The relevance of these interactions for the anticancer activity of Ga remains to be determined.

Ga may also interact with DNA by acting as a competitor with magnesium for DNA binding. It has been reported that the affinity of Ga for DNA is 100 times higher than that of magnesium [6].

It has also been shown in vitro that Ga induces chromatin condensation, which is an early step in apoptosis, a process that Ga is able to initiate, as reported by Riaz-Ul-Haq et al. [7].

According to Hedley et al. Ga inhibits replicative DNA synthesis; the major Ga specific target probably being ribonucleotide reductase [8]. The 50% inhibitory concentration for T cell lymphocytes was 120 µmol/l. In

addition, Chitambar reported that Ga binds avidly to transferrin and gives a transferrin–Ga complex and that this complex inhibits DNA synthesis by acting on the M2 subunit of ribonucleotide reductase [9]. The inhibition of DNA synthesis by Ga nitrate could result from a combination of a block on the availability of iron to ribonucleotide reductase and direct inhibition of the enzyme [10].

2.2. Modification of protein synthesis

At a concentration of Ga that inhibits cell growth, all processes of cell biosynthesis are reduced, including protein synthesis. It has also been reported that some proteins undergo a specific modulation of expression. Aoki et al. noticed that specific synthesis of several cellular proteins was markedly induced by exposure to 300 μM Ga. These proteins were defined by their molecular weights: 85 000, 71 000, 65 000, 51 000, 38 000, 30 000 and 28 000 [11].

On the other hand, Ga nitrate inhibits osteocalcin gene expression. Osteocalcin is an osteoblast-specific bone matrix protein that is thought to serve as a signal to trigger osteoclastic resorption. Reduction of osteocalcin mRNA level is observed with high selectivity, since levels of other mRNAs synthesized by ROS 17/2.8 cells are not decreased [12].

Ga increases incorporation of 3H-proline into hydroxyproline in collagenase digestible protein. It also increases levels of mRNA for fibronectin and type I procollagen chains in tumour and non-tumour cells. In short, the exposure of mesenchymally-derived cells to Ga results in an altered pattern of matrix protein synthesis that would favour increased bone formation [12,13].

Synthesis of the cellular transferrin receptor is decreased by Ga, whereas hemoglobin production is inhibited. These results provide an explanation for the development of microcytic hypochromic anemia in patients treated with Ga nitrate and suggest that the mechanism of chemotherapeutic action of Ga includes inhibition of cellular iron incorporation [14].

Ga also reduces pokeweed mitogen-stimulated immunoglobulin production by 84–100% [15].

The biological effects of Ga have also been studied in *Escherichia coli*. Ga induces synthesis of one protein (mw = 30 000) and causes a decrease in that of two others (mw = 15 000 and 28 000) [16].

2.3. Enzyme inhibition

2.3.1. ATPases

Anghileri et al. studied the inhibitory effect of Ga, at concentrations of 25–100 $\mu\text{mol/l}$, on a Mg-dependent renal ATPase [17]. The dose-dependent inhibitory effect observed could result from the competition of Ga with

magnesium. Ga inhibits H^+ -dependent ATPase as well [18].

2.3.2. DNA polymerases

Waalkes et al. [19] and Adamson et al. [20] reported that Ga nitrate inhibits the DNA polymerases of Walker 256 carcinoma cells at a concentration of 50 $\mu\text{g/ml}$. Ga nitrate also inhibits the reverse transcriptase of the virus from the Rausher leukaemia. Otherwise, Ga has no direct effect on DNA polymerase. At a concentration of 480 $\mu\text{mol/l}$ lasting 24 h, Ga nitrate inhibited DNA synthesis by 20% [8].

2.3.3. Ribonucleotide reductase

Tumour cells incubated with 2 $\mu\text{mol/l}$ of transferrin–Ga for at least 6 h showed a decrease in ribonucleotide reductase activity. This enzyme is iron-dependent, catalyses the reduction of ribonucleotides in deoxyribonucleotides and is involved in DNA synthesis. As already noted, Chitambar et al. determined that the inhibitory effect was exerted through an interaction with the M2 sub-unit [9] and that this activity could be the result of a competition of Ga with iron.

2.3.4. Tyrosine-specific protein phosphatase

At a concentration of 2–6 $\mu\text{mol/l}$, Ga nitrate inhibits tyrosine-specific protein phosphatase of human leukaemia cells and human colon cancer cells by 50%. This effect is not modified by hydrogen peroxide. Although, in Jurkat cells, Ga nitrate has no effect on tyrosine-specific protein phosphatase, the addition of hydrogen peroxide results in inhibitory activity [21]. It should be noted that no correlation was found between the growth-inhibitory activity against Jurkat and HT-29 cells and the ability to inhibit detergent-solubilized tyrosine-specific protein phosphatase. This is a new mechanism of action for Ga nitrate, but it is not known if the inhibition of tyrosine-specific protein phosphatase is related to the antitumour activity [21].

2.4. Antitubulin effects

Ga chloride mimics the effects of vincristine and inhibits the glycerol induced tubulin polymerization in a concentration-dependent manner, indicating that Ga chloride is a microtubule destabilizing agent that prevents microtubule assembly. The inhibitory effect of 250 μM GaCl_3 persists in the presence of up to 9 mM MgCl_2 , suggesting that the exogenous Mg^{++} cations absolutely required for the binding of GTP to tubulin and microtubule assembly cannot overcome the antitubulin action of Ga^{3+} ions of a higher valence. The binding of [^3H]GTP to tubulin is decreased by unlabeled GTP but markedly enhanced by GaCl_3 , especially when concentrations of this salt of 32 μM or higher are added to the reaction mixture before rather than after

the radiolabeled nucleotide. These data suggest that changes in protein conformation following GaCl_3 binding might increase the interactions of tubulin with nucleotides and vinca alkaloids. After a 24 h delay, the viability of GaCl_3 treated L1210 leukemic cells is reduced in a concentration-dependent manner at days 2 (IC50: 175 μM), 3 (IC50: 35 μM) and 4 (IC50: 16 μM). Because the concentrations of GaCl_3 that inhibit tubulin polymerization also increase the mitotic index and decrease the viability of L1210 cells in vitro, the antitubulin and antimitotic effects of GaCl_3 might contribute, at least in part, to its antitumor activity [22].

3. Cellular biology

3.1. Cell penetration and intracellular Ga distribution

Ga binds to transferrin, although it has a lower affinity than that of iron: Ga $k_a = 25 \mu\text{mol/l}$ and iron $k_a = 9 \mu\text{mol/l}$. The exchange of iron and Ga binding to transferrin has been studied by NMR. Ga displacement by iron is slow and the exchange half-life is $\approx 4.3 \text{ h}$ [23].

Transferrin containing Ga binds to its specific receptors on the cell plasma membrane without modification. It is interesting to note that tumour cells have more transferrin receptors than normal cells. After Ga enters the cell, it is transferred to cellular ferritin, as is iron itself [24,25], the transfer of Ga from protein to protein is increased by ATP and, with a lower efficacy, by ADP [26,27]. The addition of transferrin to culture medium markedly increases the toxicity of Ga [28].

Within cells, Ga is found mostly as a phosphate salt in lysosomes, [29,30]. In cell metabolism, it appears that the trivalent Ga^{3+} ion acts as an antagonist to several divalent ions including Mg^{2+} , Fe^{2+} , Zn^{2+} and Ca^{2+} [31].

Intracellular concentrations of Ga can be modified, under certain conditions, by cisplatin, salts of iron, gold and zinc [28,32–34].

3.2. Cell membrane permeability

The effects of Ga on (i) transfer of ions through the isolated human amnion, expressed as the measure of the transamniotic conductance, (ii) on ionic fluxes and (iii) on the flux ratio (mother–foetus/foetus–mother) were studied by Bara et al. [35,36]. It was observed that Ga decreased transamniotic conductance and ionic fluxes, but had no effect on the flux ratio. Since this effect on transamniotic transfer is common to Ga and other anticancer metals and is identical to that of carcinogenic metals, the cell membrane does not seem to be the target for antitumour effect. An ultrastruc-

tural study of the epithelial cells of the human amnios indicates a decrease in the intercellular space.

Nevertheless, the effect of Ga on the permeability of the plasma membrane has been measured on living K562 cells using a micro-spectrofluorimeter. Cells were first incubated with 1–10 $\mu\text{mol/l}$ Ga for 48 h, washed twice and then incubated with doxorubicin for 4 h. The preincubation with Ga induced a significant decrease ($P < 0.01$) in the intra-nuclear content of doxorubicin of 27 and 40% for Ga concentrations of 1 and 10 $\mu\text{mol/l}$, respectively, [37].

The role of Ga in the modulation of cell membrane permeability could be related to several mechanisms: alteration of the cell membrane potential, modification of electric charges at the surface of the cell membrane, a modification of ATPase activity and a decrease of the membrane pore diameter [17,35,36,38].

3.3. Effect of Ga on mitochondrial function

Ga induces an efflux of calcium from mitochondria in a dose related manner. This release is more significant when the calcium content of mitochondria is elevated [39]. Cyclosporine inhibits the effect of Ga on calcium efflux from mitochondria, suggesting that the mechanism of action of Ga may be located at the level of the mitochondrial membrane pore or may involve pyridine nucleotide hydrolysis. It should be remembered that calcium efflux is a preliminary step in apoptosis [39].

3.4. Suppression of the production of nitric oxide

The efficacy of Ga nitrate was examined in a murine model of sepsis. Sepsis was induced by treatment with 0.3 mg i.v. of *Propionibacterium acnes* followed 1 week later by 0.01 μg lipopolysaccharide (LPS) and 10 mg of D-galactosamine (GalN). Ga nitrate was injected s.c. (45 mg/kg) 24 h prior to LPS/GalN. Two hours after LPS/GalN or vehicle, plasma concentrations assay of tumor necrosis factor ($\text{TNF}\alpha$) were performed and no significant changes were observed. After 6 h, plasma concentrations of nitrate/nitrite (products of nitric oxide) were 64 ± 8 ($n = 7$), 146 ± 18 ($n = 8$), and 57 ± 8 ($n = 15$) μM . Ga suppressed the production of nitric oxide induced by the pathogen agent [40].

3.5. Matrix metalloproteinase activity

The effects of Ga nitrate on the inflammatory process was examined on matrix metalloproteinase (MMP) activity utilizing the rabbit synoviocyte cell line HIG-82. These cells were incubated with IL1 β and TPA, with and without increasing concentrations of Ga nitrate. Conditioned medium was collected and assayed for MMP activity using a synthetic substrate and substrate

gel zymography. IL β and TPA alone induced MMP activity in HIG-82 cells. A dose-dependent inhibition of IL β and TPA stimulated MMP activity by Ga nitrate at increasing concentrations was observed [41].

3.6. Cytotoxic effect

The cytotoxicity of Ga nitrate to EMT-6/UW mouse sarcoma cells growing in vitro has been assessed in terms of growth inhibition as well as cell survival (colony-forming ability). Ga is both cytostatic and lethal to cells, with some growth inhibition occurring after chronic exposure to a low concentration (10 $\mu\text{g}/\text{ml}$), which is not lethal to cells. Cell kill and growth inhibition were both observed when cells were exposed for 24 h or more to concentrations greater than 50 $\mu\text{g}/\text{ml}$. It is interesting to note that Ga, unlike most cytotoxic drugs, is effective against cells during both exponential growth and stationary plateau phase [28,33]. The cell inhibition induced by Ga chloride is both depending on the concentration and on the time of exposure. It was observed in L1210 leukemic cells exposed to Ga chloride during 2–4 days. The IC₅₀ was 175 μM after an exposure time of 48 h, but 35 μM after an exposure time of 72 h and only 16 μM after an exposure of 96 h [22].

Ga toxicity is related to intracellular concentration [9,42–44]. Ga activity is enhanced 10-fold by addition of transferrin to the culture medium, which increases the cellular incorporation of Ga [28,45].

This antagonistic effect of Ga and Fe has also been observed in human macrophages infected by pathogenic mycobacteria and thus does not appear to be selective of malignant cells, but could also counteract the proliferation of bacteria cells. It was found a concentration-dependent growth inhibition of mycobacteria within the macrophages, depending also, like for cancer cells, on the duration of the exposure of the cells to the Ga treatment. Ga induced a growth inhibition over 72 h but after a 7 day exposure, a microbicidal effect was observed (without disruption of the macrophage monolayer). This activity was also related to the action of Ga on the Fe-dependent ribonucleotide reductase and moreover the Ga-mediated growth inhibition of the mycobacterial cells was reversed by exogenous Fe, confirming the data observed in malignant cells [46].

The addition of iron to the culture medium greatly reduces Ga toxicity [28,33,47–53]; at a critical cellular concentration iron induces resistance to Ga [54]. When cells were depleted of iron, by addition of a chelator (desferrioxamine) their sensitivity to Ga was increased, but it must be added that if a little quantity of chelator remained in the culture medium, it could reduce Ga toxicity since it chelates Ga also [55].

Ga-pyridoxal isonicotinoyl hydrazone (Ga-PIH), a new compound, presents interesting activities. Its anti-proliferative activity is superior to that of Ga nitrate, its mechanism of action seems different since the addition of exogenous iron to the culture medium reverses Ga nitrate toxicity, but has a minor effect on Ga-PIH toxicity [56].

The tris(8)quinolinolatoGa(III) compound has a powerful inhibitory effect on malignant cells, about 10 times higher than Ga chloride [57].

The anionic component of the metal salt has no influence on toxicity. Chloride and sulphate have been tested and yield the same cytotoxicity [3,4]. Ga acts synergistically with paclitaxel on the MB-435 human mammary cell line under some conditions. This effect is schedule-dependent and is only observed when cells are first incubated with Ga (300 $\mu\text{mol}/\text{l}$, for 24 h), followed by paclitaxel (10 nmol/l). There is no synergy when cells are incubated with both agents simultaneously [58].

3.7. Circumvention of drug resistance

It has been reported that resistance to the antitumor agent Ga nitrate in human leukemic cells is common, since only 60% of patients respond to its treatment. This resistance is associated with decreased Ga/iron uptake, increased activity of iron regulatory protein-1, and decreased ferritin production [59]. The Ga-PIH derivative is able to overcome the resistance of lymphoid leukemic cell to Ga nitrate by delivering Ga intracellularly [60].

A novel doxorubicin-Ga-transferrin conjugate has been formulated (Dox-Ga-Tf). It exhibited approximately the same growth-inhibitory effect as doxorubicin on MCF-7 cells with IC₅₀s of 2.3 nmol/l and 1.4 nmol/l, respectively. However, in resistant MCF-7 cells, Dox-Ga-Tf reversed the resistance to free doxorubicin. The IC₅₀ was decreased 100-fold, from 9 $\mu\text{mol}/\text{l}$ with free doxorubicin to 95 nmol/l for Dox-Ga-Tf. Dox-Fe-Tf was also 10-fold more active against MCF-7 resistant cells than free doxorubicin. Compared to Ga-Tf, Dox-Ga-Tf was 500- and 3000-fold more inhibitory to MCF-7 and MCF-7 resistant cells, respectively, [61]. In summary, this interesting study showed that the reversal of resistance to doxorubicin by the Dox-Ga-Tf conjugate is mediated by (i) the transferrin receptor transmembrane transport mechanism, (ii) redistribution of doxorubicin into the nucleus of doxorubicin resistant MCF-7 cells and inhibition of MRP gene expression.

Tris(8-quinolinolato)Ga(III), is also an interesting derivative. In vitro it is 10 times more active than Ga chloride [57] and has been reported to circumvent both unicellular and multicellular resistance. Its ID₅₀ against the parent A549 cells is identical to that for a subline

induced to be resistant to etoposide, when this subline showed cross resistance to doxorubicin, cisplatin and vinblastine [62]. The so-called multicellular resistance is obtained when cells are cultured as spheroids, instead of as a monolayer on the bottom of plastic flasks; i.e. this resistance appears as soon as cells have established contacts with other cells or with the extracellular matrix. This type of resistance is named ‘multicellular’ since multiples cells are necessary for it to be observed, in contrast to resistance involving any mechanism which induces resistance in isolated cells and can therefore be named ‘unicellular resistance’ [63]. The most interesting point about tris(8-quinolinolato)Ga(III) is that its ID50 against a given parent cell line is equal whether the cells are grown as an aggregate and as spheroids. To achieve a similar activity, the concentration of etoposide had to be increased 163-fold, 35-fold for doxorubicin, 27-fold for cisplatin and 6625-fold for vinblastine.

3.8. Cell cycle

Ga chloride inhibits growth of L1210 cells by 30–70% after a 24 h incubation in vitro with 20–500 $\mu\text{mol/l}$. A modification of cell cycle distribution is observed after at least 24 h incubation with Ga: the percentage of cells in S phase was decreased, whereas the percentage of cells in the G0/1 phase was increased [64]. This effect is reversible after the cells are washed and re-incubated in fresh medium containing no drug. Although, an important amount of cell debris can be observed in the culture medium during the second incubation, indicating that a number of cells which appeared to be alive at the end of the first incubation, had already received a lethal hit and thus died during the second incubation.

On a human T lymphoblastic cell line, Hedley et al. reported that Ga induced an accumulation of cells in S phase, which indicates an inhibition of DNA synthesis, owing to a specific inhibition of ribonucleotide reductase [8].

4. In vivo studies on animals

4.1. Toxicology

4.1.1. Acute and sub-acute toxicity

Acute toxicity studies in rats showed an oral dose lethal to 50% of animals (LD50) of 1.75 g/kg for Ga nitrate, i.e. the equivalent of 0.48 g/kg of Ga, and of 2 g/kg for Ga sulphate, i.e. the equivalent of 0.33 g/kg of Ga. In mice, the oral LD50 is 2.15 g/kg for Ga nitrate, i.e. the equivalent of 0.59 g/kg of Ga, and 2.33 g/kg for Ga sulphate, i.e. the equivalent of 0.38 g/kg of Ga. Signs of toxicity did not appear immediately after Ga

administration, and these toxicities were reversed with time. During a 14-day observation, Domingo et al. reported anorexia, weight loss, reduced pupil reflex, exophthalmus, myosis and bleeding of the hands and feet [65].

The dose of Ga chloride lethal to 10% of animals, (LD10) in mice bearing a CA755 tumour is 150 mg/kg i.p. [66]. For oral administration, the LD50 of Ga sulphate is greater than 4 g/kg in rats and mice according to Cahuzac et al. [67] and Domingo et al. [65,68]. For Ga nitrate, the oral LD50 is 2.7 g/kg in mice and more than 4 g/kg in rats [69]. The low toxicity of oral doses could be due to a low bioavailability [69].

4.1.2. Chronic toxicity after injection

LD50 of Ga nitrate after daily i.p. administration, for 10 days, is 80 mg/kg/24 h in mice and 67.5 mg/kg/24 h in rats [4]. The major chronic toxicity is renal, which seems to be related to the precipitation of Ga in a complex with calcium and phosphate, which occludes the tubular lumen [70]. Administration of an osmotic diuretic, isosorbide, prior to Ga treatment resulted in the formation of fewer renal precipitates [70].

Other chronic toxicities are: weight loss, lung and liver pathologies [4]. Haematological toxicity was only an inhibition of haemoglobin synthesis, which is related to iron deficiency [14,43,70].

4.1.3. Chronic toxicity after oral administration

Oral daily doses of 10 mg/kg were administered to dogs for several months without visible toxicity, despite specific monitoring of bone marrow, kidney and liver [30]. Oral daily doses of 200–400 mg/kg of Ga chloride for 20–40 days in rats and mice induced no visible sign of toxicity [71–75].

Ga arsenide, used in the electronics industry, induces pulmonary inflammation and pneumocyte hyperplasia in rats. Decreasing the mean volume diameter of particulates of Ga arsenide resulted in an increase in its dissolution rate in vivo and thus increased the severity of pulmonary lesions. The incidence of pulmonary fibrosis, as indicated by analysis of lung 4-hydroxyproline content, was not considered statistically significant although histological examination of lung tissue revealed a mild fibrotic response [76]. This increase of lung 4-hydroxyproline in newly synthesised collagen by Ga could explain the tumour fibrosis induced by this element [30,72]. This suggests that careful monitoring of fibrosis in all patient tissues during treatment with Ga is justified.

A 6 month study of chronic toxicity in dogs, performed at doses of 20, 40, 60 mg/kg/24 h, confirmed this risk in lungs, but it depended neither on the dose, nor on the length of treatment and it did not increase mortality [31].

4.2. Gallium pharmacokinetics

4.2.1. After injection

Forty eight hours after a single i.p. administration of 135 mg/kg of Ga chloride in tumour-bearing-mice, concentrations were 40 times higher in kidneys ($2 \mu\text{mol/g}$) than in tumour ($0.05 \mu\text{mol/g}$) [77]. Tissue uptake of Ga was increased by isoprenoid [78]. Tissue uptake was also modified by simultaneous administration of other metals such as platinum [79,80] or gold [32].

4.2.2. After oral administration

Bioavailability is low after a single oral administration [69]. Nevertheless an accumulation in tissue can be observed after repeated daily administration.

In rats receiving 200 mg/kg/24 h of Ga chloride orally for 20 days, the highest tissue concentrations were observed in bones ($29.9 \pm 5.7 \mu\text{g/g}$), then in lungs ($11.5 \pm 15.3 \mu\text{g/g}$), when in plasma the highest concentration observed was 1 mg/l [75]. The tissue concentrations were comparables in kidneys ($5.9 \pm 1.4 \mu\text{g/g}$), spleen ($5.8 \pm 2.5 \mu\text{g/g}$), adrenal ($4.6 \pm 2.0 \mu\text{g/g}$), liver ($4.3 \pm 2.3 \mu\text{g/g}$) and ovaries ($2.9 \pm 1.3 \mu\text{g/g}$). The tissue concentrations were lower in muscles ($1.4 \pm 1.5 \mu\text{g/g}$), heart ($0.6 \pm 0.3 \mu\text{g/g}$) and brain ($0.3 \pm 0.5 \mu\text{g/g}$). Tissue concentrations increased with time in bones, spleen, adrenal and heart, whilst Ga plasma concentration did not increase, indicating a terminal half-life shorter than 24 h. After 5 days without administration, Ga concentrations decreased in plasma and kidneys, but were not modified in the other tissues [75].

In a study performed in tumour-bearing (C3HBA cell line) mice, the doses of Ga chloride administered orally were 200 and 400 mg/kg/24 h for 30 consecutive days. The tissue concentrations were highest in kidneys (2.03 ± 0.8 and $3.27 \pm 0.88 \mu\text{g/g}$, for the two dose levels, respectively), then in the tumour (2.16 ± 0.93 and $2.60 \pm 0.88 \mu\text{g/g}$). In conclusion, the ratio of tumour/kidney concentrations appeared less favourable as the dose of Ga was increased [74].

Ga pharmacokinetics are modified by the duration of administration. Ga concentration in C3H tumours was $38.4 \pm 30.0 \text{ nmol/g}$ at a dose of 200 mg/kg of Ga chloride daily for 21 days and $13.4 \pm 7.3 \text{ nmol/g}$ at the same dose for 42 days. In the kidneys the concentrations were $44.4 \pm 8.7 \text{ nmol/g}$ after 21 days of the same treatment and $14.9 \pm 2.1 \text{ nmol/g}$ after 42 days [74]. The same decrease in tissue concentration with longer duration of treatment was also observed in dogs with spontaneous mammary tumours [30]. It is interesting to note that such a decrease in tumour concentration could be apparent rather than real. During treatment with Ga, the cell number in the tumour decreased, as fibrosis was increasing. As a result, the extracellular content of Ga would be diluted, whereas the intracellular content would be constant [30].

The Ga concentration in a tumour depends on the tumour volume. Thus, at equal doses, tumour concentrations of Ga were higher when the tumour volumes were smaller [81].

New Ga complexes seem to have a higher bioavailability [82] such as tris(8)quinolinolatoGa(III) compound [82,83] and also the Ga maltolate [84].

The bioavailability of six Ga salen compounds (tetradentate Schiff-base Ga complexes) was also studied after oral gavage in rats. It was observed a rapid oral absorption and maximum Ga levels in plasma were achieved within 1 h of administration. The amount absorbed in 4 h was comparable to that observed following intraperitoneal injection of Ga nitrate. Bioavailabilities were 69, 91, 46 and 89% for salens in which X=OH (dimer), Cl, OAc and NO₃, respectively. In comparison, Ga nitrate administered orally at the same dose (0.067 mmol/kg) as the salens did not show appreciable absorption. Salens with X=OAc and substituents of Cl or N(CH₃)₂ on the A ring drastically reduced oral absorption. Replacing the ethylenediamine group (B ring) with diaminepropane also reduced oral absorption to below effective Ga levels ($< 1 \mu\text{g/ml}$) as with oral Ga nitrate [85].

4.3. Biological effects

After chronic administration of Ga, the concentrations of magnesium, calcium, iron and zinc were decreased within tissues [34,42,71,74,75]. Competition between Ga and magnesium was first reported by Anghileri in 1975 [86]. Competition of Ga with these metals could explain, at least in part, the mechanism of action of this element [34,48,71,87–97].

The action of Ga on bone metabolism was studied primarily because it decreases the hypercalcemia associated with cancer [98–102]. Ga inhibits osteoclastic activity and decreases hydroxyapatite crystal formation, with absorption of Ga onto the surfaces of hydroxyapatite crystals. In addition, there is an increase of collagen synthesis related to the bone concentration of Ga and an increase of bone tissue formation in vitro [103–111].

Tissue fibrosis [29,30,71,76] and modification of vascular permeability have been also reported [112]. It was also noted that Ga nitrate was able to increase the type I collagen, the fibronectin mRNA and the collagen protein levels in bone and fibroblast cells [13].

4.4. Antitumour activity

4.4.1. After parenteral administration

Administration of Ga nitrate i.p. for the 10 days following sub-cutaneous transplantation of a solid tumour in mouse and rats inhibits tumour growth by more than 90% in six out of eight experimental rodent

tumours, at doses between 30 and 60 mg/kg/24 h. Very few differences were noticed between Ga chloride and sulphate [20].

Ga is also active on 256 Walker sarcoma transplanted i.p. The median survival time is increased by 138%, as compared to control. Conversely, Ga is not active against several leukaemia cell lines (L1210, K1964, P388) and Ehrlich carcinoma transplanted i.p. [20].

Ga nitrate, administered i.p. at a dose of 37.5 mg/kg/24 h for five consecutive days, starting 5 days after transplantation of a Lewis lung carcinoma, inhibited both tumour growth and formation of lung metastases. At a lower dose (23.1 mg/kg/24 h) Ga is not active against the primary tumour, but significantly decreases the number of lung metastases. However, there was no difference between the two Ga doses in survival 14 days after tumour transplantation. Besides, at a lower dose of 11.6 mg/kg/24 h there was no significant decrease in the weight of the primary tumour and no decrease in metastases. Nevertheless, the number of mice surviving was increased, as compared to controls [34].

For the highest doses, zinc concentrations in liver and tumour were significantly decreased in treated mice, while they remained normal in plasma and other tissues. The antitumour activity of Ga is increased when there is a deficit of zinc, although it must be pointed out that mice with a lower amount of zinc in their diet have a higher mortality. Zinc status appears therefore to have an important influence on efficacy and toxicity of Ga treatment [34].

The efficacy of Ga chloride has been compared at two different phases of tumour growth, during exponential growth and during the plateau phase in mice bearing the adenocarcinoma CA755. Ga was administered i.p. at a single dose of 135 mg/kg (90% of the LD10) or at a dose of 21 mg/kg twice a day, during 5 days. Both treatments were more efficient when administered during exponential growth, with a rapid and significant decrease of tumour volume. Treatment during the plateau phase was less efficient and erratic [66].

4.4.2. After oral administration

A significant decrease of tumour growth was reported in mice bearing a C3HBA tumour, with an oral daily dose of 400 mg/kg of Ga chloride in drinking water. The treatment began the same day that tumour cells were grafted. Nevertheless a delay was necessary before a significant difference in tumour volume as compared to control mice was observed. This effect on tumour growth disappeared when tumours reached the plateau phase [73].

The tris(8)quinolinolatoGa(III) compound appeared to be very active in an experimental model, with a reduction of more than 50% of the volume of the tumour, without any significant toxicity [113].

5. Clinical studies

5.1. Gallium nitrate i.v.

In phase I or II studies, Ga nitrate has been used in patients refractory to conventional chemotherapy. The drug is administered intravenously, either as a bolus every 3 weeks or as continuous infusion of 5–7 days every 3 or 4 weeks. For the i.v. bolus, the maximum dose was 750 mg/m² because of renal toxicity [114–117]. Ga pharmacokinetics, were altered in patients with acute renal dysfunction and in patients who had received multiple doses of Ga or other metal chemotherapy. Phase II trials failed to show any efficacy for this treatment protocol [117–119]. Ga concentrations were 130 times higher in kidneys than in tumour and this lack of specificity could explain the negative results reported [114].

By using a protracted infusion during 5–7 days, a daily dose of 100–300 mg/kg can be used without renal toxicity [120–124]. With this protocol a Ga plasma concentration greater than 1 mg/l can be achieved [120]. Clinical trials indicate that such a protocol is effective against cancer hypercalcemia [98–100,102].

Ga is ineffective in melanoma according to Casper [125], metastatic colorectal cancer according to Canfield [126], head and neck cancer [127], prostate cancer [128], kidney cancer [129], ovary cancer [130] and in breast cancer [131]. Preliminary studies in bladder carcinoma [132], carcinoma of the urothelium [133] and lymphomas [122,134,135] were initially promising, but it has not been studied in further detail in lymphoma. With regard to urothelial cancers, these studies were not pursued in the USA because of ocular toxicity and also because the manufacturer stopped production of Ga nitrate.

In combination with vinblastine and ifosfamide, in a phase II trial, Ga was very effective in metastatic urothelial carcinomas at a dose of 300 mg/m²/24 h for five consecutive days, every three weeks. The objective response rate was 67%, including 41% complete responses. However, the median duration of the responses was short at 20 weeks. This was associated with a high degree of toxicity, with granulocytopenia grade 3 and 4 in 56% patients, despite the use of growth factors. Furthermore, 11 out of 27 patients had anaemia grade 3 or 4 and 4 patients had renal function alteration grade 3 or 4. In addition, there were 3 patients with hypocalcemia grade 3 or 4, 3 with thrombocytopenia, one encephalopathy and one temporary blindness. One patient died during the study [136].

It was noted in a study of 8 patients that Ga had modest clinical activity in prostate cancer in the elderly [137]. In a clinical trial on 21 patients with non-small cell lung cancer, it appeared that a short infusion of Ga nitrate achieving high peak plasma concentrations re-

sulted in little efficacy. One partial response was reported, 4 patients had stable disease and 16 progressed [138].

In another study, it was reported that vinblastine, ifosfamide, and Ga nitrate (VIG) was an active regimen in patients with advanced urothelial carcinoma. Toxicity was significant but acceptable, nevertheless, patients with significant cardiac disease (especially arrhythmias) should be treated with extra care [139]. The same VIG protocol in heavily pretreated ovarian cancer patients yielded 5/14 patients achieving a partial response i.e. a response rate of 36%. The median response duration was 14 weeks. Toxicity was primarily hematologic, with anemia and leukopenia being most significant. There were no treatment-related deaths [140].

A series of 40 patients received the maximally tolerated dose of paclitaxel with and without filgrastim (G-CSF), administered as a 24-h intravenous infusion, after a 120-h infusion of Ga nitrate at a fixed dose of 300 mg/m²/24 h. One partial response was reported in a patient who had thymoma and one complete response in a patient who had colon cancer [141].

Another interesting schedule of treatment with low doses of Ga nitrate has also been proposed, with 40 mg administered as a sub-cutaneous injection once daily for 2 weeks, especially for the treatment of bone metastases but the definitive results have not yet been published [142].

5.2. Oral gallium chloride

Ga chloride can be administered orally at doses between 100 and 1400 mg/24 h as a single agent without major toxicity. This regimen yielded partial responses in ovarian cancer, associated with Ga plasma concentration greater than 600 µg/l [143–145]. In patients with lung cancer, the Ga plasma concentration was less than 600 µg/l and no response was observed. Bioavailability was too low following oral administration of Ga chloride and the antitumour activity insufficient to recommend the use of Ga as monotherapy [145].

Nevertheless, Ga uptake is selective for tumour and even more so for metastasis, compared to kidneys, after oral administration as compared to intravenous injection [145]. Because of this aspect of tissue pharmacokinetics, oral administration of Ga has been suggested in order to potentiate radio- or chemotherapy in lung cancer.

A clinical study indicated that the optimal dosage of oral Ga chloride was 400 mg/24h [145]. Another showed that at this dose, during and between courses, Ga potentiates the action of cisplatin and etoposide [146]. The percentage of partial responses was more significant in patients receiving Ga plus cisplatin and etoposide, as compared to those receiving only the two

classical anticancer drugs. However, a delayed toxicity appeared after three courses of this triple chemotherapy. To avoid this cumulative toxicity, a dose adjustment has been proposed for cisplatin and for Ga. The purpose of the dose adjustment was to achieve a constant area under the curve (AUC) of total platinum concentration versus time from cycle to cycle. Several assays of total platinum plasma concentration were performed in order to modify the cisplatin dosage to reach the target AUC. The AUC value for the whole infusion was between 80.000 and 100.000 µg/l h. The result was an absence of major toxicity, with a clinical response comparable to that of the previous study [108,146–149]. This dose adjustment was performed during several courses without toxicity and thus permitted an increase in the number of courses.

5.3. Oral gallium maltolate

The pharmacokinetics of Ga maltolate have been studied in healthy patients receiving a single administration. Four dosages have been studied: 100, 200, 300 and 500 mg. Each dosage was administered to three subjects. The oral bioavailability of Ga maltolate was better than after an oral administration of Ga chloride and estimated to be of 25–57%. The dominant half-life of elimination for Ga was ≈ 17–21 h, suggesting a potential for once-per-day dosing [84].

5.4. Combination of Ga with other cytotoxic agents

Preclinical studies have demonstrated synergy between Ga and paclitaxel [58], Ga and gemcitabine [150], Ga and vinorelbine [151], Ga and hydroxyurea [9], Ga and fludarabine [55] or Ga and interferon-α [152]. It should be intriguing to confirm this synergistic antineoplastic activity in the clinic [153].

6. Conclusion

Ga is the second metal ion, after platinum, to be used in cancer treatment. Even though the antitumour effects of Ga nitrate were demonstrated a long time ago, the optimum schedule of administration of Ga compounds still needs to be determined.

An important consideration in increasing the efficacy of Ga compounds is the schedule of administration. It was shown that a synergism could occur *in vitro* between Ga and several anticancer drugs and interferon-α. In addition, it was shown that Ga had to be administered before the exposure to paclitaxel and not simultaneously in order to obtain the best synergistic effects.

The oral administration of Ga chloride allows a continuous cellular exposure to the Ga metal ion. A

long duration of administration of combined therapy is required to take into account delayed antitumour effects, as well as the induction of tumour fibrosis, and therefore to optimise the improvement in survival.

New Ga compounds with a better bioavailability are now under clinical investigations and could improve the anticancer activity first demonstrated with Ga nitrate or Ga chloride.

Reviewers

Christopher R. Chitambar, M.D., Professor of Medicine, Division of Hematology/Oncology, Medical College of Wisconsin, 9200 W. Wisconsin Avenue-FEH, Milwaukee, WI 53226-3596, USA.

Dr Brian Leyland-Jones, Department of Oncology, DCS IDB CTEP, McGill University, Gerald Bronfman Center, 546 Pine Ave W, Montreal, PQ H2W 1S6, Canada.

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Biographies

Collery Philippe R., born 1951, Ay, Marne, France. Oncologist. Education: Medical Studies 1967–1974; M.D, 1976; Internal Medicine Specialist's degree, 1980; Oncology Degree, 1987; Pharmacology Degree, 1987 (Ph.D). Appointments: Intern (major), University Hospital Reims 1974–1978. Lecturer, University Hospital Reims 1978–1982, Assistant Cancer Institute, Reims 1982–1984, Medical Doctor University Hospital Reims 1984–2000, HRD (Habilitation à diriger des recherches) 1998, Oncologist Polyclinique Maynard, Corsica 2000-; Publication: co-editor, *Metal Ions in Biology and Medicine*, John Libbey Eurotext, Paris, 6 issues (one volume every other year since 1990).

Bernard Desoize took his degree in Pharmacy in 1970 and his doctorat d'état in 1976. He was fellow at Columbia University, New York, during one year and half. He became professor of Biochemistry and Molecular Biology in 1981 in Reims, F, where he is currently. He was simultaneously biologist during 19 years in Anticancer Centre of Reims. He is a member of the EORTC PAMM group. He has authored 120 articles, mainly in the field of anticancer drugs: new drugs, clinical pharmacokinetics and cell resistance.