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Invited review

The therapeutic potential of iron-targeting gallium compounds in human disease: From basic research to clinical application

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ABSTRACT

Gallium, group IIIa metal, shares certain chemical characteristics with iron which enable it to function as an iron mimetic that can disrupt iron-dependent tumor cell growth. Gallium may also display antimicrobial activity by disrupting iron homeostasis in certain bacteria and fungi. Gallium's action on iron homeostasis leads to inhibition of ribonucleotide reductase, mitochondrial function, and changes in proteins of iron transport and storage. In addition, gallium induces an increase in mitochondrial reactive oxygen species in cells which triggers downstream upregulation of metallothionein and hemoxygenase-1. Early clinical trials evaluated the efficacy of the simple gallium salts, gallium nitrate and gallium chloride. However, newer gallium-ligands such as Tris(8-quinolinolato)gallium(III) (KP46) and gallium maltolate have been developed and are undergoing clinical evaluation. Additional gallium-ligands that demonstrate antitumor activity in preclinical studies have emerged. Their mechanisms of action and their spectrum of antitumor activity may extend beyond the earlier generations of gallium compounds and warrant further investigation. This review will focus on the evolution and potential of gallium-based therapeutics.

Contents

Abbreviations: Tf, transferrin; TfR, transferrin receptor; RR, ribonucleotide reductase; ROS, reactive oxygen species; MT, metallothionein; HO, heme oxygenase-1.

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1. Introduction

The discovery of gallium in 1875 is credited to Paul-Emile Lecoq de Boisbaudran who described it as two distinct bands on spectroscopy while studying sphalerite ores (zinc sulfide) [1]. While the metal was felt to have been named in honor of France (Gallia), there is some speculation that the discoverer may have named it after himself, with the derivation of gallus being Latin for 'le coq' (rooster).

Gallium compounds have been of interest to the medical community for decades; the spectrum of activity of gallium is summarized in Fig. 1. As early as 1931, Levaditi et al. reported that gallium tartrate eradicated syphilis in rabbits and *trypanosoma evansi* in mice [2]. However, further evaluation of gallium's potential as a therapeutic agent appears to have stalled until the late 1970s when gallium nitrate entered clinical trials as an NCI-designated investigational agent (NSC 15200) after its antitumor activity was demonstrated in rodents [3]. Since then, gallium compounds, ranging from simple gallium salts (gallium nitrate) to more complex structures of gallium-ligands, have advanced in preclinical and clinical investigations; these agents have shown therapeutic activity in cancers, infections, and inflammatory conditions. The ability of gallium to localize in tumors and sites of inflammation had been previously observed in animal studies; this led to the development of the radiogallium ^{67}Ga scan for the detection of cancers in humans [4–6]. Although the ^{67}Ga scan has largely been replaced by positron emission tomography (PET) scans that measure $^{[18]}$flurodeoxyglucose uptake by tumors [7], ^{68}Ga-labeled pharmaceuticals are emerging as sophisticated tools for tumor imaging [8,9]. Apart its place in the medical field, gallium, as gallium arsenide, is used extensively in the electronics industry as a component of semiconductors, light emitting diodes, and solar energy applications [10].

While gallium has no known function in human physiology, the chemical properties that it shares with iron allow it to bind to iron-containing proteins, including the iron transport protein transferrin (Tf) [11]. Thus, malignant cells and microorganisms may be tricked into incorporating gallium in place of iron for iron-dependent processes essential for cell viability and growth. However, rather than facilitate iron-dependent cellular function, gallium disrupts it. As a result, the interaction between gallium and iron-proteins can be exploited for therapeutic purposes in cancers and infections (recently reviewed in reference [12]). This paper will discuss the progression of gallium compounds from preclinical studies to clinical trials and will provide a perspective on the therapeutic potential of the newer gallium-based compounds in human disease.

2. Chemistry

Gallium is a group IIIa metal, atomic number 31 in the periodic table of elements. It exists in the earth's crust at a concentration of 5–15 mg/kg and is obtained as a byproduct of extraction of aluminum and zinc ores. It is a silvery white metal with a melting point of 28.7646 °C, a temperature which enables it to melt while being held in the hand. The transition of gallium from solid to liquid state has been entertainingly presented on YouTube as "the vanishing spoon trick" in which a spoon made of solid gallium is shown to disappear while being used to stir warm water in a glass. Gallium is one of the few metals that will expand by approximately 3% as it cools and can diffuse into the lattice of most metals to form alloys. Certain properties of gallium are shared with iron (III); the octahedral ionic radius for Ga^{3+} is 0.620 Å compared with 0.645 Å for high spin Fe^{3+} while the tetrahedral ionic radius is 0.47 Å and 0.49 Å for Ga^{3+} and Fe^{3+}, respectively. The ionization potential and electron affinity values for Ga^{3+} are 64 eV and 30.71 eV, respectively, while for high spin Fe^{3+} they are 54.8 eV and 30.65 eV, respectively [13]. One distinct difference between the two metals is that iron can exist in a divalent [Fe (II)] or a trivalent [iron (III)] state. In contrast, gallium exists only as gallium (III). Thus, iron is redox active while gallium is not.

3. Transport, distribution, and cellular uptake of gallium

Insights into the mechanisms of gallium uptake by tumors and its handling by the body were gained with the development of the ^{67}Ga scan. Intravenously-injected ^{67}Ga citrate was found to bind almost exclusively to Tf in the circulation, thus indicating that gallium is transported in the blood in a manner similar to iron [14]. The addition of Tf to culture medium was shown to promote the uptake of ^{67}Ga by myeloma and other cell lines further indicating that gallium shares both extracellular transport and cellular uptake mechanisms with iron [15]. That this cellular uptake mechanism occurs by Tf receptor (TfR)-mediated uptake of Tf-Ga was confirmed by the demonstration that monoclonal antibodies against the TfR inhibited cellular ^{67}Ga uptake in vitro and in vivo [16,17]. In addition, induction of TfR expression in mutant Chinese hamster ovary (CHO) that lack endogenous TfRs produced an increase in their uptake of ^{67}Ga [18]. The TfR-mediated uptake of gallium explains why malignancies such as lymphoma and others that express high levels of TfRs can be successfully imaged with ^{67}Ga scans [19,20]. Beyond this, both iron and gallium may also enter cells by TfR-independent transport systems that appear to share certain similarities since gallium can enhance Tf-independent cellular iron uptake and vice versa [21]. However, the TfR-independent cellular uptake mechanisms for iron and gallium must not be entirely similar since the uptake of iron by this system requires the reduction of Fe(III) to Fe(II) by a cell surface reductase or the generation of free radicals [22,23]. On the other hand, Ga(III) is not reduced to Ga(II) which suggests that its TfR-independent entry into cells may involve other mechanisms such as interaction with low-molecular-weight transporters.

Despite gallium's binding to Tf in the circulation and its cellular uptake by the TfR, gallium's pharmacokinetics is different from that of iron. A comparison of ^{67}Ga-citrate and ^{59}Fe citrate distribution in the body showed that after its intravenous injection in healthy individuals, the elimination rate constant for ^{67}Ga citrate was 50-fold slower than that for ^{59}Fe citrate and that ^{59}Fe was cleared from the blood at a more rapid rate than ^{67}Ga [24]. The distribution of ^{59}Fe was largely confined to hematopoietic tissues for hemoglobin production. ^{59}Fe uptake by the sacrum, liver, spleen, and heart followed classically described ferrokinetics and its uptake progressively declined after achieving a peak uptake at 24 h after intravenous injection [24,25]. In contrast, the volume of ^{67}Ga distribution in the body was approximately 6 times that of iron. ^{67}Ga rapidly accumulated in the same tissues as iron in the first 24 h following injection but then progressively increased in these tissues with time [24]. This pattern is noted with ^{67}Ga scanning for tumors where ^{67}Ga progressively accumulates at tumor sites while it washes out in other non-malignant tissues. [26]. In another study, Nelson et al. examined the distribution of ^{67}Ga in patients and reported that following its intravenous injection, the highest concentrations of ^{67}Ga in descending order were in the spleen, kidney, adrenals, marrow, liver, bone, and lymph nodes [26].

The intracellular distribution of gallium is only partly understood. Studies which tracked the localization of ^{67}Ga in rat hepatoma in vivo after animals were injected with ^{67}Ga revealed that ^{67}Ga concentrated in microsomes and lysosomes [27–29]. A 45 kD-gallium-binding protein in lysates from rat hepatoma cells was isolated [30,31], however, this protein was not further characterized. Additional studies demonstrated that ^{67}Ga concentrated in