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Metal drugs become targeted

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Since ancient times, metal compounds have been utilised successfully in medicine to treat diverse diseases including cancer. With the discovery of cisplatin in the 1960s by Barnett Rosenberg, platinum drugs became central to systemic therapy of multiple malignancies. Nowadays, platinum compounds still constitute a mainstay of systemic oncological treatment regimens leading, depending on the cancer type, to high response rates or even cure.[1 2] Nevertheless, major hurdles for cancer cure by this so-called 'conventional chemotherapy' remained unsolved including primarily the adverse effects based on the cytotoxic activity also against healthy tissues and the rapid development of drug resistance due to the enormous genomic and epigenetic flexibility and adaptability of the malignant cells. Additionally, based on the elucidation of the human genome and the availability of high-throughput sequencing methods, precision medicine concepts have been entering into oncological treatment strategies moving conventional chemotherapies out of focus. Accordingly, the research community during the last few decades believed that precise elucidation of oncogenic driver mechanisms would allow to treat patients with late stage cancer with higher precision, avoiding damage of the non-malignant tissues and less efficient resistance development. These promises have been delivered in part and especially in the field of haematology, while in patients with solid tumours—even after initial responses—targeted compounds often fail due to rapid resistance development. Recently, cancer immunotherapy based on immune checkpoint inhibitors has again revolutionised systemic cancer therapy, delivering breathtaking results in some tumour types with extremely high mutation rates like melanoma, bladder cancer and smoking-associated lung cancer. Nevertheless, only a minority of patients with cancer significantly benefits from this modern immune-based treatment options. Consequently, combination approaches with conventional and targeted therapies are currently screened, initiating also a revival of classical mutagenic chemotherapy approaches to enhance cancer immunogenicity.[3]

In parallel, it became obvious that the view of anticancer metal drugs as mere cytotoxic agents toxifying all proliferating cells might be too short-sighted and that they might also hit precise cancer targets. One of the most impressive proofs of that concept was the elucidation of the molecular mechanism underlying the antileukaemic effect of arsenic trioxide (ATO), the oldest metal remedy in human use. This cytotoxic compound selectively targets the oncogenic nucleophosmin-retinoic acid receptor (NPM-RAR) alpha fusion gene product, hence releasing the blockade of terminal differentiation in acute promyelocytic leukaemia cells.[4] Accordingly, also other clinically used metal drugs have been investigated closer with surprising results. Thus, it has been demonstrated that oxaliplatin induces immunogenic cell death of cancer cells resulting in a vaccination effect while cisplatin does not.[5 6] Considering that DNA platination is widely assumed as the central mode of action for both compounds, this example impressively visualises that our view on conventional chemotherapy might often be oversimplifying.

Accordingly, a multitude of novel metal compounds have been synthesised and tested for their anticancer activity also in clinical studies. Surprisingly, despite this enormous effort, novel anticancer metal compounds were not approved for clinical use more recently. One reason might be that during the design but also the evaluation of metal compounds by synthetic chemists, the exact mode of action is not worked out in detail impeding optimisation approaches. Besides platinum and gold, anticancer metal drugs development primarily has focused on ruthenium compounds.[7] The attractiveness of this platinum group metal to develop

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tumour-specific drugs lies primarily in its redox nature allowing ruthenium oxidation states +II and +III at physiological conditions. As Ru(III) is distinctly less reactive as compared with Ru(II), prodrug strategies are possible based on activation by reduction in the reductive environment of solid tumours.

Burris *et al* present now in *ESMO online* an interesting first-in-man clinical phase I study of a Ru(III) prodrug termed IT-139 (former NKP-1339 or KP1339).[8] In case of this novel metal complex, a dual prodrug design strategy has been taken. Besides activation by reduction from Ru(III) to Ru(II), IT-139 is systemically inactivated by efficient binding to serum proteins like albumin and transferrin in the blood stream.[9] Accordingly, the in vitro cytotoxicity of the compound is moderate as long as sufficient levels of fetal calve serum are present, while the half maximal inhibitory concentration values dramatically drop under serum starvation. Consequently, while healthy tissues with intact blood vessels are unaffected, leaky tumour vessels allow the protein-bound drug to enter the interstitium of the tumour tissue, a concept called 'enhanced permeability and retention' or EPR effect.[10] From there the still inactive, protein-bound prodrug is preferentially taken up by malignant cells via endocytosis to assuage the tumour's limitless need for anabolic building blocks.

The tumour-targeting concept seems to work in case of IT-139 based on the observation of clinical response or disease control in the current phase I study, lack of neutropaenia and minimal adverse effects. Generally, the low toxicity of IT-139 allowed application of relatively high IT-139 doses with a maximum tolerated dose (MTD) of 625 mg/m^2 for a longer treatment time. Hence, IT-139 represents a first-in-class ruthenium-based small molecule that—besides promising activity and tumour specificity in preclinical studies—has delivered strong indications for an adequate therapeutic window also in the clinical phase I setting. In contrast, the only other ruthenium compound tested in a clinical phase I/II study before, namely, imidazolium-trans-dimethylsulfoxide-imidazoletetrachlororuthenate or NAMI-A, allowed application of distinctly lower doses only. While at the MTD of 300 mg/m^2/day, no clinical responses and only one stable disease were observed; higher doses resulted in painful blisters on hands and feet and corticosteroid premedication was required to prevent hypersensitivity reactions.[11] Interestingly, NAMI-A exerted only antimetastatic effects in preclinical animal models, while IT-139 was targeting all types of lesions including the primary tumour.[12] These observations already suggest differences in tissue distribution and probably also mode of action. While at earlier studies, DNA was considered the main target of all anticancer metal drugs, this hypothesis has been revised meanwhile. Hence, IT-139 shows also intracellularly a distinct protein-binding pattern and, in good agreement with uptake as protein-conjugate, accumulation, for example, in the lysosomes. Interestingly, this serum protein-bound uptake mechanism also strongly reduces the affinity of the drug to ATP-binding cassette (ABC) transporter efflux pumps including ABCB1.[13] However, IT-139 might not only be able to circumvent drug resistance mechanisms, its mode of action even seems to involve the blockade of important cellular protection mechanism. Recently, IT-139 was demonstrated to block stress-induced upregulation of glucose-regulated protein of 78 kDa (GRP78, also termed BIP).[14 15] GRP78 represents a major chaperon of unfolded protein response (UPR) upregulated in multiple therapy-resistant tumours and its inhibition renders tumour cells vulnerable to endogenous metabolic and radical stress, hypoxia and the effects of cytotoxic compounds.[16] Moreover, malignant cells spontaneously exhibit enhanced levels of protein damage and consequently UPR as well as endoplasmic reticulum (ER) stress. In addition to GRP78, we recently found also other important chaperones including major heat-shock proteins to be affected by IT-139 exposure of cancer cells in vitro (manuscript in preparation). These data suggest that IT-139 generally targets cellular protein repair and, together with redox-based induction of radical oxygen species (ROS), mediates both tumour cell apoptosis and resistance reversion in a 'two-edged sword' fashion. This fits well with the synergistic activity of this compound with drugs inducing protein damage but also ROS production in vitro.

The activity of IT-139 in the study by Burris *et al* is relatively moderate with a 26% disease control rate and only one partial response in a patient with colon cancer. However, it has to be kept in mind that the majority of patients enrolled had received multiple lines of treatment before inclusion and exhibited progressive, therapy-refractory disease. Moreover, the main objective of a phase I trial is definitely not to prove efficacy. Interestingly, out of the 10 patients with disease control by IT-139, three patients suffered from neuroendocrine tumours (NET; two carcinoids and one gastrinoma, out of five NET patients in the study). All three patients were stable with non-progressive disease when they went off the study, in one case even after 98 weeks. This tumour selectivity is interesting as NET are widely resistant to established systemic therapies including chemotherapy and targeted drugs. Moreover, it has been recently suggested that pancreatic NET are characterised by particularly high intrinsic ER stress levels.[17] Consequently, it will be interesting whether this single drug anti-NET activity holds true in a phase II setting. Nevertheless, it seems that blocking the stress-induced upregulation of GRP78 by IT-139 alone is obviously not sufficient to achieve massive tumour responses in the majority of these therapy-resistant patients. Therefore and based on the complete lack of neutropaenia, IT-139 might be ideally suitable for combination approaches with chemotherapeutics or targeted compounds. Synergistic activity of IT-139 with several targeted and chemotherapeutic compounds has already been observed in preclinical in vivo models and the evaluation in clinical studies is desirable. To put it in a nut-shell, anticancer metal compounds have finally

arrived in the world of molecularly targeted cancer therapy.

Correction notice This article has been corrected since it first published. The title has been changed from 'Metal drugs go targeted' to 'Metal drugs become targeted'.

Competing interests None declared.

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REFERENCES

1. Kelland L. The resurgence of platinum-based cancer chemotherapy. *Nat Rev Cancer* 2007;7:573–84.
2. Jungwirth U, Kowol CR, Keppler BK, *et al*. Anticancer activity of metal complexes: involvement of redox processes. *Antioxid Redox Signal* 2011;15:1085–127.
3. Gotwals P, Cameron S, Cipolletta D, *et al*. Prospects for combining targeted and conventional cancer therapy with immunotherapy. *Nat Rev Cancer* 2017;17:286–301.
4. Zhang XW, Yan XJ, Zhou ZR, *et al*. Arsenic trioxide controls the fate of the PML-RARalpha oncoprotein by directly binding PML. *Science* 2010;328:240–3.
5. Galluzzi L, Buqué A, Kepp O, *et al*. Immunological effects of conventional chemotherapy and targeted anticancer agents. *Cancer Cell* 2015;28:690–714.
6. Terenzi A, Pirker C, Keppler BK, *et al*. Anticancer metal drugs and immunogenic cell death. *J Inorg Biochem* 2016;165:71–9.
7. Muhammad N, Guo Z. Metal-based anticancer chemotherapeutic agents. *Curr Opin Chem Biol* 2014;19:144–53.
8. Burris HA, Bakewell S, Bendell JC, *et al*. Safety and activity of IT-139, a ruthenium-based compound, in patients with advanced solid tumours: a first-in-human, open-label, dose-escalation phase I study with expansion cohort. *ESMO Open* 2017;1:e000154.
9. Bytzek AK, Koellensperger G, Keppler BK, *et al*. Biodistribution of the novel anticancer drug sodium trans-[tetrachloridobis(1H-indazole) ruthenate(III)] KP-1339/IT139 in nude BALB/c mice and implications on its mode of action. *J Inorg Biochem* 2016;160:250–5.
10. Greish K. Enhanced permeability and retention (EPR) effect for anticancer nanomedicine drug targeting. *Methods Mol Biol* 2010;624:25–37.
11. Leijen S, Burgers SA, Baas P, *et al*. Phase I/II study with ruthenium compound NAMI-A and gemcitabine in patients with non-small cell lung cancer after first line therapy. *Invest New Drugs* 2015;33:201–14.
12. Bergamo A, Sava G. Linking the future of anticancer metal-complexes to the therapy of tumour metastases. *Chem Soc Rev* 2015;44:8818–35.
13. Heffeter P, Pongratz M, Steiner E, *et al*. Intrinsic and acquired forms of resistance against the anticancer ruthenium compound KP1019 [indazolium trans-(tetrachlorobis(1H-indazole)ruthenate (III)) (FFC14A). *J Pharmacol Exp Ther* 2005;312:281–9.
14. Lizardo MM, Morrow JJ, Miller TE, *et al*. Upregulation of glucose-regulated protein 78 in metastatic cancer cells is necessary for lung metastasis progression. *Neoplasia* 2016;18:699–710.
15. Gifford JB, Huang W, Zeleniak AE, *et al*. Expression of GRP78, master regulator of the unfolded protein response, increases chemoresistance in pancreatic ductal adenocarcinoma. *Mol Cancer Ther* 2016;15:1043–52.
16. Roller C, Maddalo D. The molecular chaperone GRP78/BiP in the development of chemoresistance: mechanism and possible treatment. *Front Pharmacol* 2013;4.
17. Kliieser E, Illig R, Státtner S, *et al*. Endoplasmic reticulum stress in pancreatic neuroendocrine tumors is linked to clinicopathological parameters and possible epigenetic regulations. *Anticancer Res* 2015;35:6127–36.