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Sequential Administrations of a Vascular-Disrupting Agent, High-Intensity Focused Ultrasound, and a Radioactively labeled Necrosis Avid Compound for Eradicating Solid Malignancies

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Abstract

Radical treatment of malignant solid tumors should aim to be less traumatic, precise, and effective. OncoCiDia, as a noninvasive, sequential dual-targeting, small-molecule, broad spectrum anticancer theranostic approach, may fulfill these requirements of solid cancer (Onco) treatment with both tumoricidal (Ci) and diagnostic (Dia) effects. However, it is unlikely to cure patients with cancer, especially those with large and irregular tumors and with tumors residing in certain organs, such as the brain and pancreas, because of insufficient necrosis generation. To amplify ablative efficacy, this shortcoming could be overcome by combining high-intensity focused ultrasound (HIFU) with the use of a vascular-disrupting agent (VDA) and a radioactively labeled necrosis avid compound (NAC), such as ^{131}I-Hypericin (^{131}I-Hyp), which are the first and second targeting drugs used in OncoCiDia. This study proposes the combined use of OncoCiDia and HIFU (Onco-HIFU-CiDia) as a synergistic treatment for malignant tumors to achieve a curative multimodality and multidrug regimen for patients with solid cancers, in accordance with the current trend of cancer patient care.

Keywords

vascular-disrupting agent, hypericin, HIFU, OncoCiDia, internal radiation, broad spectrum anticancer, targeted therapy

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Abbreviations

BH, boiling tissue section; BBB, blood–brain barrier; CCH, cavitation cloud tissue section; CA4P, combretastatin A 4-phosphate; Dia, diagnostic; HIFU, high-intensity focused ultrasound; ^{131}I-NACs, ^{131}Iodine-labeled necrosis avid compound; ^{131}I-Hyp, ^{131}I-Hypericin; NAC, necrosis avid compound; Ci, tumoricidal; SPECT, single-photon emission computed tomography; VDA, vascular-disrupting agent

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Introduction

Currently Available Therapies for Solid Malignancies

Currently, several techniques are available for the treatment of malignant solid tumors, each has their own disadvantages. (1) Surgical resection is the most effective method, as it can be radical; however, its efficacy is limited in cases of incomplete resection or tumor metastasis.[1] (2) Although chemotherapy and radiotherapy are commonly used in tumor treatment, they lack specificity and can often cause serious side effects.[2] (3) On the contrary, virtual cancer ablation therapies, such as high-intensity focused ultrasound (HIFU), radiofrequency ablation, microwave therapy, laser therapy, and cryotherapy, are more accurate in targeting tumor lesions due to imaging guidance.[3] However, these methods are often characterized by incomplete treatment, with the survival of even a few cancer cells, tumor recurrence can occur. (4) Molecular anticancer drugs have improved targetability but have a narrow application scope and tendency for drug resistance.[4] (5) Immunotherapies, which rely on activated immune cells or antibody-mediated mechanisms to treat cancers, have limited availability and are often costly.[5] (6) Internal targeted tumor radiotherapy, which uses targeted molecular drugs labeled with a high-energy radionuclide, often fails to achieve the cumulative radiation dose required for radical cancer treatment (normally > 50 Gy) owing to inherent defects, such as poor targeted distribution, low affinity, and short retention time with these molecules.[6]

Consequently, the above treatments based on a single method and agent are often associated with a high chance of tumor recurrence. To tackle this problem, low-molecular-weight anticancer drugs with high tumor targetability, broad spectrum of antitumor activity, and long-lasting effects should be explored, for example, using prior-induced tumor necrosis as a common target for delivering a necrosis avid compound (NAC) labeled with a radioactive isotope to irradiate nearby residual viable tumors within a penetration distance. Additionally, a combination of anticancer techniques may be used.

OncoCiDia, a Novel pan-Anticancer Theranostic Approach, is an Efficient, Accurate, Economical, and Practical Strategy for the Treatment of Solid Malignancies

In view of the shortcomings of current cancer therapies, a novel strategy, namely OncoCiDia, has been developed with the aim of curing cancer using rational drug combinations.[7] Based on a patented "targeted radiotherapy",[8] this approach requires only 1 episode in 2 consecutive days that contains sequential intravascular deliveries of a tumor vascular-disrupting agent (VDA) and a radioactively labeled NAC.[9–13]

Figure 1 illustrates the schematic mechanism of action of OncoCiDia. First, a VDA, such as combretastatin A 4-phosphate (CA4P), is intravenously infused as the first drug to target the tumoral blood vessels (ie, depolymerizing the tubulin of cytoskeleton in their abnormal endothelium) and block tumor nutrient supply, thereby creating large areas (up to 55%-90%)[14] of ischemic necrosis (Figure 1A to C). However, some cancer cells on the edge of the tumor survive and regrow, owing to the blood supply from adjacent normal vessels, which has imposed a bottleneck for the VDA clinical development and calls for a solution to eliminate the residual cancer cells. Next, the VDA-induced tumor necrosis provides an ideal target for the second drug, namely ^{131}Iodine-labeled necrosis avid compound (^{131}I-NAC), such as ^{131}I-Hypericin (^{131}I-Hyp), which is administered 1 day after the first drug is administered. Being able to selectively bind to necrosis, Hyp thus brings iodine-131 with high-energy β-particles and an effective penetration distance of 2 to 3 mm around the necrotic tumor, thereby exerting continuous internal ionizing irradiation on the adjacent residual cancer cells, ideally leading to complete tumor ablation (Figure 1D and E). OncoCiDia is currently undergoing early phase clinical trials in both veterinary and human patients.[15,16]

OncoCiDia has several advantages. First, since both the drugs are small molecules, they have high permeability and low immunogenicity. Second, as the first VDA drug targets tumoral blood vessels instead of individual tumor receptors or antigens, all solid malignancies with abnormal vessels are subjected to tumor necrosis, which become universal secondary targets that render pan-anticancer strategy. Third, the second OncoCiDia drug, radio-iodinated hypericin (^{131}I-Hyp), has high necrosis-targeting specificity and affinity with necrosis distribution over 3.34% ID/g (comparable to or higher than that of iodine-131 in thyroid cancers) and regional retention for weeks to months, leading to persistent local targeted radiotherapy with an estimated cumulative radiation dose of 5000 Gy owing to the relatively long half-life of iodine-131 of over 8 days.[9] Fourth, β-particles released from ^{131}I-Hyp that irradiate cancer cells of 2 to 3 mm in depth while sparing the healthy tissue beyond this depth for safety reasons, along with low-energy γ-rays emitted from iodine-131 enabled nuclear imaging, such as single-photon emission computed tomography (SPECT),

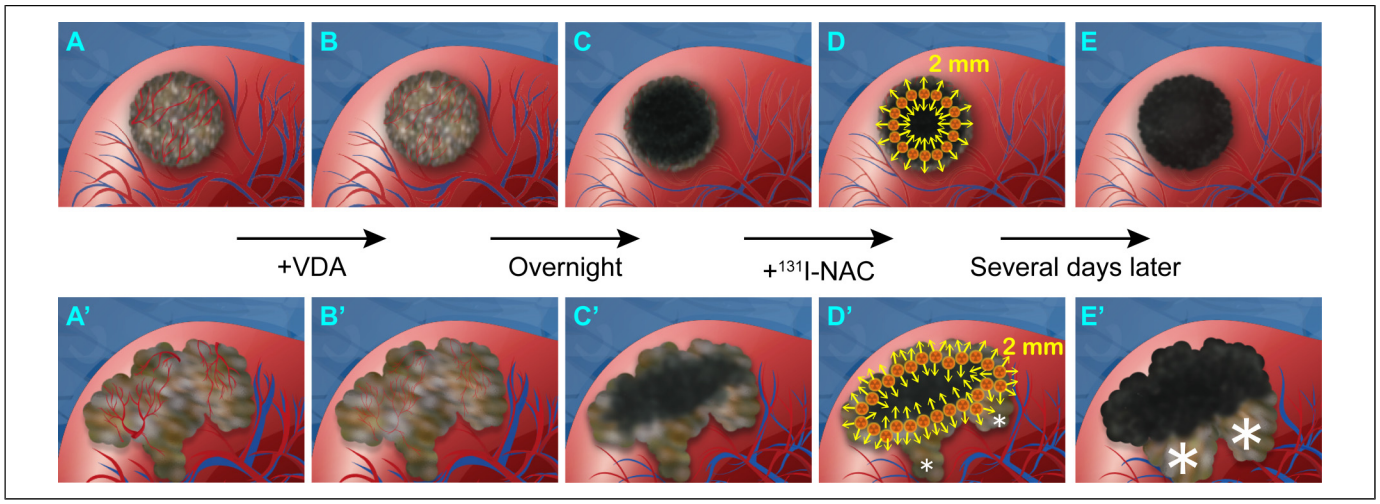

Figure 1. The schematic mechanism of action of OncoCiDia. A solid tumor in the liver is illustrated. Cancer cells are nourished by abundant tumoral and surrounding blood vessels (A). These tumor vessels are blocked from 15 min after the start of intravenous VDA (eg, CA4P) infusion (B), resulting in a large area of central ischemic or hemorrhagic necrosis, but peripheral tumor cells close to normal tissues can still externally obtain blood supply with nutrients for regrowth (C). One night post VDA infusion, ^{131}I-NAC (eg, ^{131}I-Hyp) is administrated, which can selectively accumulate in central necrosis, particularly at the viable-necrotic tumor interface, whereby emitting high-energy β-particles with 2 to 3 mm penetration distance (D). The residual cancer cells are killed by constant crossfire β-particles from ^{131}I-Hyp with an 8-day decay half-life with a high cumulative radiation dose but without collateral damage to normal cells (E). However, the tumor might recur if it is large and irregularly shaped (A'). Tumor blood vessels can also be blocked by a VDA (B'); the vast majority of cancer cells inside tumors are also dead, but some residues, especially those deeply intertwined with the surrounding normal tissue at the edge of the tumor may still survive (C'). As ^{131}I-NAC accumulates in necrotic tumor, the distance of 2 to 3 mm radiation is too short to fully cover those residual live tumor cells located in the peripheral protrusions (marked by small white asterisks) (D'), and later, the residual live cells proliferate leading to tumor recurrence (marked by big white asterisks) (E').
Abbreviations: CA4P, combretastatin A 4-phosphate; ^{131}I-NAC, ^{131}Iodine-labeled necrosis avid compound; ^{131}I-Hyp, ^{131}I-Hypericin; VAC, vascular-disrupting agent.

for monitoring the treated primary and/or metastatic lesions over a period of 1 to 2 months. Thus, OncoCiDia can simultaneously diagnose, treat, and monitor solid cancer. Preclinical experiments have revealed that OncoCiDia not only diagnoses and treats (theranostics) but also inhibits tumor growth, improves clinical symptoms, and prolongs survival.[9,10]

Disadvantages of OncoCiDia

Although a contraindication for ascites and pleural forms of diffusive metastases, where primary targets of abnormal tumor blood vessels are absent,[9] OncoCiDia has certain disadvantages in the treatment of solid tumors. For instance, in large and irregularly shaped tumors, as well as those located in the pancreas[17] and brain, ischemic necrosis caused by a VDA of the first OncoCiDia drug tends to be insufficient, with residual tumor layers being too thick to be penetrated by the secondary ^{131}I-NAC targeted irradiation of 2 mm in depth, resulting in incomplete ablation and tumor relapse (Figure 1A' to E'). Mathematical modeling suggests that 1 episode of OncoCiDia might cure small tumors with a diameter less than 2 cm, while its curability rate could decrease for tumors that are 2 to 10 cm in diameter.[18] This may happen because large and irregularly shaped tumors often have protruding edges more extensively intertwined with surrounding normal tissues (Figure 1A' to E'). Even when they are cut off from their tumoral blood supply, cancer cells at these junctions can survive and recur by invading normal nutrient-rich tissues. Owing to the complex anatomy of the pancreas, its blood supply can originate from the celiac artery, common hepatic artery, splenic artery, and upper and lower mesenteric arteries. Consequently, a VDA can only briefly block the blood supply to the pancreatic tumor rather than cause necrosis due to prolonged irreversible ischemia.[17] The brain is characterized by the presence of the blood–brain barrier (BBB), which may impair the access of VDA to the tumor, resulting in insufficient tumor necrosis compared to that in extracranial cancers. In these cases, the efficacy of the second targeting drug (eg, ^{131}I-Hyp) is limited. Therefore, further research is warranted to develop optimal therapeutic regimens for different types of solid tumors, particularly for those that are difficult to treat.

Advantages and Disadvantages of HIFU and its Complementary Potential for OncoCiDia

HIFU treats soft tissues by focusing high-intensity ultrasound pulses noninvasively into a cigar-shaped focal area (in millimeters) in the depth of body tissues and quickly generates a temperature over 70 °C, thereby causing tissue coagulation necrosis.[19] Its advantages include visibility, noninvasiveness,

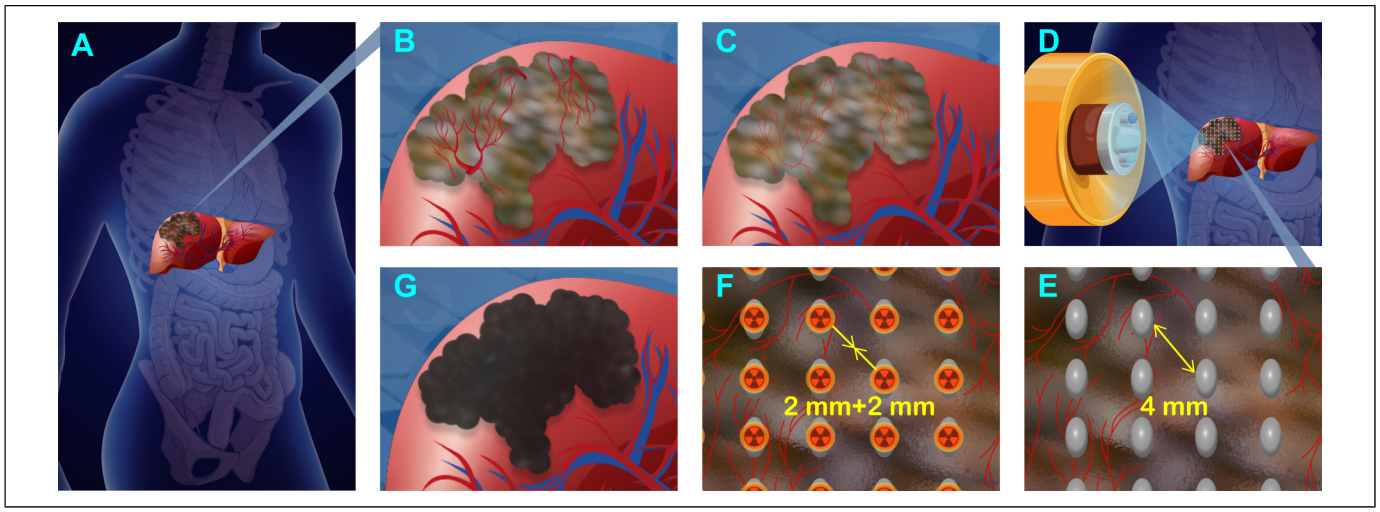

Figure 2. Schematic diagram of the novel strategy Onco-HIFU-CiDia that combines HIFU with OncoCiDia constituents. As a large, irregularly shaped tumor (A), abundant tumoral blood vessels are distributed within the tumor (B), and these tumor blood vessels are specifically blocked within 15 min onwards after VDA injection (C). With reduced heat sink effect caused using a VDA, HIFU is subsequently carried out (D), producing multiple necrotic foci arrayed in a matrix having a distance of 4 mm among the foci (less than twice of the radiation penetration distance), adapted to the shape of the tumor. However, residual cancer cells may remain within the interlesional gaps (E), and ^{131}I-NAC or ^{131}I-Hyp releases β-irradiation covering all the residual live tumor cells in these gaps (F), thereby effectively eliminating malignant cells, preventing cancer relapse, and enhancing cure rate (G).
Abbreviations: ^{131}I-NAC, ^{131}Iodine-labeled necrosis avid compound; ^{131}I-Hyp, ^{131}I-Hypericin; HIFU, high-intensity focused ultrasound; VDA, vascular-disrupting agent.

and precision. HIFU can generate numerous evenly distributed, diffusive, and localized necrotic foci in tumors to kill cancer cells while sparing normal tissue. Combined with the first targeting drug (VDA) used in OncoCiDia, HIFU could be more potent in producing necrotic foci in large and irregularly shaped tumors, and possibly also in pancreatic[17] and brain tumors than OncoCiDia alone.

The disadvantages of HIFU include (i) blood flow within the tissue causes a heat sink effect during HIFU,[20] which may reduce the thermal energy crucial for thorough coagulative necrosis and leave residual tumor cells that may regrow and (ii) cancer cells between coagulated foci may escape from thermal damage irrespective of the density of the HIFU matrix.

Both the disadvantages of HIFU therapy can be compensated using the first (VDAs) and second (^{131}I-NACs) targeting drugs of OncoCiDia. VDAs have recently been found to have a temporary vasoconstrictor effect,[21,22] and the heat sink effect is known to be reduced by vasoconstrictive drugs.[23,24]

Perspectives

Based on the aforementioned analyses, the optimized combination of broad spectrum anticancer theranostic strategies can be acronymized as Onco-HIFU-CiDia, denoting the combination of HIFU and OncoCiDia components in the proper order. This strategy may address the need in clinical oncology for improved radical treatment of large and irregularly shaped tumors and difficult-to-treat pancreatic and brain tumors and solve problems, such as unresectable tumors, poor targeting specificity, narrow antitumor spectrum, and reduce recurrence rates.

The proposed mechanism of action of Onco-HIFU-CiDia, as shown in Figure 2, is as follows: (i) the first targeting drug (VDA) of OncoCiDia function as both a virtual tumor necrotizing agent and a vasoconstrictor to cause ischemic tumor necrosis and to minimize the heat sink effect for boosting HIFU efficacy (Figure 2A to D); (ii) HIFU focally "burns" live cancer cells in the tumor as well as adjacent tissues, while keeping the distance among the necrotic foci at 4 mm in the matrix (Figure 2E); and (iii) the second targeting drug (^{131}I-NACs, eg, ^{131}I-Hyp) of OncoCiDia administered overnight after necrosis formation causes persistent targeted radiotherapy on all residual cancer cells (Figure 2F and G). Since the maximal distances among the necrotic foci are 4 mm, the high-energy particles emitted by ^{131}I-NAC from HIFU-induced necrosis can fully cover the area to destroy any residual live tumor cells by crossfire radiation (Figure 2E and F). Since ^{131}I-NAC is retained in the necrotic foci, it continuously emits β-particles into the surrounding tissues to reach a lethal cumulative radiation dose well above 50 Gy but causes negligible collateral damage to healthy tissue owing to their ideal effective penetration range of 2 to 3 mm (Fig. 2F). Furthermore, the treated tumor can be visualized using SPECT/CT; hence, Onco-HIFU-CiDia is a theranostic modality.

Discussion

Both HIFU and OncoCiDia are emerging anticancer modalities, each with their own advantages and disadvantages. They complement each other and can synergistically amplify their total therapeutic potential if properly integrated into the upgraded form of Onco-HIFU-CiDia.

In this new combination, both the efficacy and application scope of HIFU will be improved with the assistance of VDA. Previously, clinicians were concerned that blood flow in tissues could dissipate the generated heat during HIFU treatment, causing insufficient thermal effects for tumor ablation.[20] Such a heat sink effect may spare a large number of live tumor cells after HIFU treatment, leading to recurrence later. Further increasing the power output to increase the temperature may cause skin burns and pain, making analgesic and fractionated treatment compulsory.[25] These shortcomings have restricted the application of HIFU in treating malignant tumors, limiting its use to the treatment of benign tumors and the beauty and weight reduction industries. By introducing a VDA shortly prior to the procedure, the HIFU ablative efficacy could be substantially boosted, thereby reducing the need for both fractionation and painkillers during benign and malignant tumor treatment. If the density of the HIFU matrix is sufficiently set, this new combination of Onco-HIFU-CiDia would theoretically result in complete necrosis over the entire treated area of difficult-to-treat malignant tumors. Therefore, the application scope of HIFU can be extended from common fields, such as beauty and weight reduction and benign tumor treatment, to advanced fields, such as radical treatment of solid malignancies.

In addition to the aforementioned conventional HIFU, histotripsy is a nonthermal focused ultrasound therapy that uses a microsecond (cavitation cloud tissue section, CCH) or millisecond (boiling tissue section, BH) pulse protocol to generate clouds of cavitation bubbles, leading to precise nonthermal tumor ablation. The released specific tumor-associated antigens within the acellular debris trigger the modulation of the immune system. Although immunomodulation is the most promising strategy in terms of long-term patient benefit, it is currently the least predictable tumor ablation therapy with benefits that are not fully understood.[26] Residual cancer cells, without mechanical fractionation, may recur. Histotripsy will similarly benefit from our proposed synergetic treatment with subsequent internal radiation from ^{131}I-NAC, while the first step of VDA perfusion will not be needed.

In combination with HIFU, OncoCiDia can overcome its intrinsic shortcomings. In OncoCiDia alone, only half of the β-particles emitted from ^{131}I-NAC retained in central necrosis is utilized to eradicate the peripheral residual cancer cells, while the other half eradicates the central necrosis that is already dead (Figure 1D and D'). This feature also impairs the ability of OncoCiDia to treat large and irregular tumors. Although the penetration range of β-particles is predetermined by physics, the position of the radiation source can be optimized. Once OncoCiDia is integrated with HIFU, ^{131}I-NAC from the evenly distributed necrotic foci emits β-particles in all directions, efficiently killing the live cancer cells among the foci. If the distance between 2 hot sources is set at 4 mm, then the entire tissue can be covered by the multilateral irradiation from the β-particles with a 2 to 3 mm penetration range (Figure 2E and F). Therefore, the combined use of OncoCiDia and HIFU may more efficiently block the proliferation of live tumor cells than using either alone, thereby achieving a radical treatment outcome.

Conclusion

In this article, we have proposed the logical combined use of OncoCiDia and HIFU to obtain a synergistic effect for the treatment of solid malignant tumors and to achieve an upgraded anticancer regimen, Onco-HIFU-CiDia, for improved rates of radical treatment outcomes. It has several advantages, namely more noninvasive than traditional surgery, more precise than chemo- and radiotherapy, and higher rates of a successful radical treatment than various minimally invasive therapies. Based on the integration of modern medicine and engineering, Onco-HIFU-CiDia may produce a synergistic effect rather than a simple overlapping effect. Further laboratory research and clinical trials are warranted to develop such novel anticancer strategies.

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

Our manuscript did not require an ethical board approval because it did not contain human or animal trials.

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