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Near-Infrared Photoimmunotherapy of Malignancy

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ABSTRACT

In the contemporary era, there has been a marked escalation in the frequency of malignant neoplasms, posing a substantial threat to the health and welfare of humans. Despite the array of therapeutic modalities currently employed, cancer treatments have yet to reach a pinnacle of effectiveness. Standard interventions, including surgical resection, radiation treatment, and chemical therapeutics, although capable of curbing the proliferation of neoplastic cells, are frequently accompanied by considerable morbidity. The adoption of near-infrared photoimmunotherapy represents an innovative therapeutic paradigm, which selectively eliminates cancerous cells with heightened accuracy, minimal invasiveness, and straightforward application. The potential for this treatment approach to be merged with supplementary medicinal substances exists, enhancing its curative impact. An exhaustive examination of the latest progress in cancer therapy utilizing near-infrared light-based immunotherapy is delineated in this document, including research performed both in China and across the globe. This analysis aims to establish a comprehensive database, aiding in the practical utilization within the clinical sphere and bolstering the pursuit of additional scholarly exploration within the field.

KEYWORDS

NIR-PIT; Malignancy; OSCC; Cancer

1. INTRODUCTION

Malignancy has become a principal worldwide healthcare challenge, exerting profound effects on the domain of public health and wellbeing. This disease occupies a prominent position among the top global causes of death [1]. In the current year 2023, the frequency of cancer cases is escalating annually, a fact supported by the latest statistics released by the World Trade Organization (WTO). The origins of these deadly growths remain partially elusive, and although therapeutic options are few, those afflicted typically endure a decrease in life quality coupled with substantial fatality figures. The records indicate around 20 million instances of cancer, with an extra estimated 9 million cases lying beyond these documented figures. The innovative treatment approach known as near-infrared photoimmunotherapy, abbreviated as NIR-PIT, represents a departure from traditional cancer treatment methods such as surgical intervention, chemotherapy, or radiation therapy [2], carving a unique niche in the therapeutic landscape. The defining characteristics of this technique encompass elevated safety margins, potent therapeutic outcomes, pronounced tumor targeting, minimal invasiveness, and simplified procedural execution, propelling NIR-PIT to the vanguard of worldwide oncological investigation and therapeutic breakthroughs. This exhaustive examination is committed to shedding light on the intrinsic mode of operation, compiling the progress within ongoing clinical investigations, and charting future directions for the exploration of Near-Infrared Photoimmunotherapy (NIR-PIT). The fundamental aim is to highlight the healing potentials of NIR-

PIT, serving as a method to enhance the therapeutic impact of cancer therapy, while also providing an underlying source of information for future associated clinical research endeavors.

2. MECHANISMS OF NEAR-INFRARED PHOTOIMMUNOTHERAPY

The innovative therapeutic method known as Near Infrared Photoimmunotherapy (NIR-PIT) signifies a paradigm shift in the realm of oncological interventions [3]. The core concept of this innovation is based on the antibody-photoresorption conjugation (APC) process, during which a particular monoclonal antibody (McAb) zeroes in on tumor cell membrane antigens and merges with the activatable by light silica-phthalocyanine pigment, IRDye700DX (IR700). Upon exposure to 690 nm near-infrared radiation, IR700 preferentially adheres to the excessively expressed analogous receptors present on the membrane of cancerous cells, precipitating rapid and precise disruption of the membrane. The preferential activation of apoptosis is triggered within the designated cells by this maneuver, simultaneously provoking an instantaneous immunological reaction. The selective impairment inflicted upon the cellular membrane of the chosen cells not only initiates apoptosis but also prompts an abrupt defensive immune reaction [4]. Therapeutic measures focused on light-specific targets form the bedrock of this treatment paradigm. The strategy currently employed merges the principles of light-based therapy with those of immune system enhancement techniques. The fundamental principles contributing to therapeutic effectiveness involve physical and chemical therapeutic impacts, the stimulation of immunogenic cell mortality in conjunction with the discriminative eradication of cells that suppress immunity, along the enhanced permeability and retention (EPR) phenomenon.

2.1. Physicochemical Therapeutic Activity

The photoactive substance IR700 lacks inherent phototoxicity or cytotoxicity and possesses hydrophilic characteristics. Release of unattached IR700 from APC enables swift removal through urinary excretion without detectable toxicological manifestations. Activation by near-infrared radiation prompts the substance to demonstrate robust cytotoxic activity against malignant cells. The synthesis of APC-antigen complexes, a product of the interaction between mAb-IR700 conjugates and tumor-associated antigens, such as EGFR and HER2, is induced to participate in a photochemical ligation upon illumination with non-thermal NIR light at 690 nm—the wavelength corresponding to IR700's activation. Concurrently, the antibody-antigen complex alters and leads to the revelation of IR700's hydrophilic side chains, instigating a rapid shift of the remaining molecules into a state marked by high hydrophobicity, alongside modifications in aggregation and solubility properties. The shift promotes the emergence of minute perforations in the cell membrane, thus undermining its architectural coherence. Hence, the integrity of target proteins is compromised, concurrently triggering an osmotic disequilibrium that prompts a swift deluge of water into the cellular structure. The occurrence triggers swift cellular distension, culminating in cell rupture and subsequent ejection of the cell's internal substances. The proposed theory suggests that structural harm to the membrane, caused by mechanical strain, acts as the primary catalyst for the activation of photodiodes through near-infrared photoimmunotherapy (NIR-PIT). The lethal route inherent in NIR-PIT is distinguished by its dissimilarity to conventional photodynamic therapy (PDT).In contradistinction to PDT, which predominantly triggers necrotic cellular demise through the creation of singlet oxygen species and reactive oxygen species (ROS), facilitating the leakage of lysosomal contents into the cytoplasmic matrix, NIR-PIT functions via an unparalleled mode of cytotoxic action. The cytotoxic impact linked to this route demonstrates a reduced intensity in comparison to membrane destruction and is further adjusted by the oxygen tension present in the tumor microenvironment [5]. The therapeutic impact of Near-Infrared Photoimmunotherapy (NIR-PIT) is contingent upon the oxygenation level of the tumorous tissue. Conversely, the selective cytotoxic action of NIR-PIT facilitates its repetitive

deployment for the eradication of residual or disseminated tumors, with minimal or no adverse effects on neighboring healthy tissue [6].

2.2. Immounogenic Cell Death

NIR-PIT, beyond mere cancer targeting, possesses the capability to bolster the immune system's reactivity by focusing on particular immune cell subsets. This enhancement is executed through two pivotal pathways: the onset of immunogenic cell death (ICD) and the strategic elimination of cells that suppress immunity. The immunogenic nature of NIR-provoked cell death arises as cellular contents, including those unique to tumors, are briskly emitted into the tumor's microenvironment upon cell lysis. Consequently, there's an increase in the expression of danger signals such as heat shock protein (HSP), calreticulin, adenosine triphosphate (ATP), and high mobility group box 1 (HMGB1). These identifiers present the tumor-specific antigens to T lymphocytes, governing the maturation of dendritic cells (DCs) within the TME, and stimulating dormant or inactive naïve CD8T cells [7]. HSP70's capacity to adhere to tumor antigens and engage with Toll-like receptors (TLRs) may facilitate the activation of cells responsible for antigen presentation. This engagement prompts the destruction of cancer cells through the expansion of cytotoxic T-cells [8], tackling cancer cells that escape the direct impact of NIR-PIT and promoting further ICD. This mechanism has the potential to establish long-term immunity memory [9]. Consequently, NIR-PIT stands apart from traditional immunotherapies [10], as it is not thwarted by issues of antibody heterogeneity, inefficient delivery, or immune engagement [11]. The liberation of several neoantigens may also invert apoptosis [12], prompting newly activated CD8T cells to acknowledge and react to a multitude of cancer antigens[13], leading to proliferation and systemic activation. This, in turn, stimulates the body's immune response and reinforces immunity, culminating in the selective eradication of suppressive immune cells. This method incurs significantly fewer autoimmune side effects than systemic cancer immunotherapies. The procedure can be initiated by directing towards surface antigens distinct to various cell types, such as CD25, which can instigate cytotoxic T-cell activity [14].

2.3. Super-Permeability and Retention Effect (SUPR)

The near-infrared photoimmunotherapy (NIR-PIT) technique exhibits a distinctive influence on tumor vascular architecture. Enhanced permeability and retention (EPR) effect, characterized by increased vascular permeability and subsequent retention of macromolecules within the tumor interstitium, is a common phenomenon observed in the majority of tumor vasculatures due to their inherent leakiness. Following NIR-PIT administration, there was a swift and marked enhancement in vascular permeability within the tumor's vasculature. Following the administration of NIR light, necrosis was observed in the cancer cells adjacent to the NIR-PIT-bound vasculature, which subsequently led to the formation of a discrete compartment between the vessel and the residual tumor mass boundary. The observed phenomenon leads to an elevation in blood volume, accompanied by vasodilation, a subsequent decrement in intratumoral pressure, and a diminished rate of blood flow. The findings indicate a significant enhancement in permeability, which exceeds the magnitude typically associated with the Enhanced Permeability and Retention (EPR) effect. The phenomenon characterized by significantly augmented permeability and retention properties is referred to as the super-enhanced permeability and retention effects, abbreviated as SUPR. The observed effect manifested within a time frame of minutes following NIR-PIT therapy and persisted for approximately 8 hours. The enhanced permeability observed with near-infrared photoimmunotherapy (NIR-PIT) via the substantial uptake and permeation ratio (SUPR) is markedly superior to the modest effect elicited by the EPR phenomenon. In contrast to the EPR effect, which demonstrates a permeability increase of less than 5% relative to normal tissue, the SUPR associated with NIR-PIT elicits a significant augmentation in vascular permeability. This enhancement facilitates the expedited delivery of nanomedicines to the tumor microenvironment [15]. The integration of NIR-PIT with nanoscale anticancer formulations has been demonstrated to elicit a superior therapeutic efficacy

compared to the individual treatments. This enhanced effect supports the direct cytotoxicity achieved through PIT.

2.4. Molecular Targets of NIR-PIT

The multipronged approach of NIR-PIT is designed to cope with a variety of cancers by concentrating on different markers such as EGFR, CD44, PD-1and the CD146 molecule found in melanoma. The versatility of this method lies in the straightforward adjustment of antibodies to switch the target, ensuring optimal performance with minimal complexity.

The receptor for epidermal growth factor (EGFR), deemed pivotal for the efficacy of NIR-PIT, not only acts as a fundamental benchmark for cellular growth but also drives a range of physiological and pathological cellular responses through its role in proliferation and apoptosis prevention. Upon binding with EGF, this transmembrane glycoprotein, a derivative of proto-oncogene activity, triggers signaling cascades crucial for the aggressive behaviors of cancer cells, including proliferation, migration, and metastasis. EGFR stands as a significant biomarker in the diagnosis and treatment of tumors, engaged in pathways that govern cell demise and often found to be excessively expressed across multiple tumor types, including colorectal, lung, breast, ovarian, cervical, bladder, esophageal, gastric, cerebral, neck, and endometrial cancers. Notably, its overexpression in head and neck cancers, particularly in oral carcinogenesis, surpasses 90%, far outstripping that in other solid malignancies. Research conducted by Yang and colleagues demonstrated that EGFR expression in oral squamous cell carcinoma tissues greatly exceeded that in non-malignant tissues, indicating its significance in OSCC progression. Xu and team further illuminated the EGFR/PI3K/HIF-1α pathway's role in OSCC, revealing its manipulation of glycolysis through pyruvate dehydrogenase kinase 1 upregulation. EMT, a critical process in tumorigenesis, was linked by Walter and associates to EGFR activation, leading to enhanced EMT expression and heightened metastatic potential in cancer cells. An investigation by V. Costa and peers established that EGFR amplification is more frequently observed in advanced stages of tumors, irrespective of age. The HER2 protein, a member of the EGFR tyrosine kinase receptor family, is implicated in cell proliferation and motility and is overexpressed in a fifth of breast cancer cases, as well as in small-cell lung carcinomas, correlating with adverse prognoses. Takahashi Kazuomi and colleagues uncovered the efficacy of trastuzumab, an anti-HER2 antibody, in HER2-targeted NIR-PIT therapy, inhibiting growth and extending survival in HER2-positive contexts [16]. Similarly, the research team led by Taki Shunichi, et al.Utilized the immune checkpoint molecule, programmed death ligand 1 (PD-L1), as a target for near-infrared photoimmunotherapy (NIR-PIT) to ascertain that localized PD-L1 targeting via NIR-PIT augments anti-tumoral immune responses, thereby delineating an additional pathway for the advancement of targeted cancer immunotherapeutic strategies [17]. The selective targeting of D44 and DIR-PIT has been empirically validated.D44 and CD133 antigens represent viable targets for the selective elimination of breast cancer and glioblastoma stem cells while sparring normal stem cells that express these markers in other bodily tissues, thereby suppressing tumor regenerative processes. Aki Furusawa's research demonstrated that CD29-targeted near-infrared photoimmunotherapy (CD29-PIT) exhibits enhanced efficacy in inhibiting tumor proliferation, selectively impacting a greater number of cancerous cells. This study positions CD29 as a promising therapeutic target for melanoma, particularly in the context of combination therapy with existing immunotherapies, such as anti-CTLA4 treatment [18]. Circulating tumor cells (CTCs) are hypothesized to play a pivotal role in the facilitation of tumor metastasis. Thus, the administration of NIR-PIT therapy directed at CTCs may result in a decrease of CTCs within the vasculature through repeated NIR light exposure to superficial blood vessels, potentially inhibiting tumor metastasis, enhancing patient survival rates, and extending the duration of disease-free intervals.

3. PROGRESS OF CLINICAL RESEARCH ON NEAR-INFRARED PHOTOIMMUNOTHERAPY

3.1. In Head and Neck Tumors

Oral squamous cell carcinoma (OSCC), frequently referred to as oral squamous carcinoma, represents the predominant malignant neoplasm within the oral cavity, comprising over 90% of all squamous cell carcinomas occurring in the head and neck region. Globally, it ranks as the sixth most prevalent form of cancer. The neoplasm exhibits a highly invasive nature and is predisposed to lymph node metastasis, contributing significantly to elevated morbidity and mortality rates. Kato Takuya and colleagues... The study examined the efficacy of near-infrared photoimmunotherapy (NIR-PIT) targeting human epidermal growth factor receptor (EGF)--expressing murine oropharyngeal carcinoma cells, specifically the mEERL-hEGFR cell line. Cells expressing CTLA4.The findings revealed that the immunogenicity of single-molecule targeted therapies, specifically NIR-PIT directed against either hEGFR or CTLA4, was comparatively lower than that of other single-molecule targeted therapies. PIT targeting solely the prostate-specific membrane antigen (PIT) failed to elicit inhibition of tumor progression in the context of poorly immunogenic murine EERL-hEGFR tumors. Conversely, the application of a dual-targeted strategy involving both CTLA4 and hEGFR in near-infrared photoimmunotherapy (NIR-PIT) markedly suppressed tumor growth and extended survival, culminating in a complete remission rate of 38%. Following the administration of dual-targeted near-infrared photoimmunotherapy (NIR-PIT), a significant reduction in the population of cells expressing CTLA4, predominantly regulatory T cells (Tregs), was noted. Concurrently, an elevated CD8+/Treg ratio within the tumor microenvironment was observed, indicative of an augmented host antitumor immune response [19]. Moreover, the dual-targeted near-infrared photoimmunotherapy (NIR-PIT) induced antitumor immune responses in distal, untreated tumors of the same histological type. This investigation indicates that the concurrent application of Near-Infrared Photoimmunotherapy (NIR-PIT) and CTLA4-targeted NIR-PIT represents a potentially efficacious novel therapeutic approach for the treatment of cancer, particularly in contexts where tumors exhibit low immunogenicity and are refractory to monotherapy with NIR-PIT alone. The findings contribute a novel conceptual framework for the management of oropharyngeal carcinoma, as demonstrated in the research conducted by Takuya Kato and colleagues. Assessed the therapeutic efficacy of employing near-infrared photoimmunotherapy (NIR-PIT) for the depletion of myeloid-derived suppressor cells (MDSCs).The methodology employed led to the preferential depletion of myeloid-derived suppressor cells (MDSCs) within the tumor microenvironment, with a notable impact demonstrated in an experimental bilateral tumor model [20]. Numerous clinical case studies, in conjunction with experimental evidence, have corroborated the therapeutic efficacy of Near-Infrared Photoimmunotherapy (NIR-PIT) in the treatment of head and neck squamous cell carcinoma. For instance, Isaku Okamoto and colleagues conducted a series of experiments... The study detailed the case of a male patient in his 70s diagnosed with maxillary gingival cancer, who underwent treatment via photoimmunotherapy, integrated with a precision navigation system. Additionally, a 76-year-old male suffering from laryngeal cancer received a therapeutic regimen consisting of radiation therapy and surgical intervention. Both interventions have yielded clinically acceptable therapeutic outcomes [21]. Makino Takuma and colleagues... Near-infrared photoimmunotherapy (NIR-PIT) was executed on a patient affected by a non-squamous cell carcinoma (non-SCC) within the head and neck region. After two rounds of NIR-PIT therapy, the residual tumor mass examination revealed the presence of minute, unattached clusters of tumor cells. Immunohistochemical analysis revealed that the epidermal growth factor receptor (EGFR) was positively expressed in the remaining tumor cells of the specimen. Tumor cells were exposed to a sufficient dose of radiation to induce necrotic cell death [22]. Daisuke Nishikawa's study presented two instances of oropharyngeal cancer that were treated utilizing Near-Infrared Photoimmunotherapy (NIR-PIT). A 77-year-old male patient, previously treated for hypopharyngeal cancer with transoral resection of the tongue root, subsequent radiochemotherapy,

and neck dissection, presented with a recurrence at the tongue root during a subsequent transoral resection for tongue cancer. This patient had previously undergone an attempted transoral resection for tongue cancer. Following 13 months of treatment with NIR-PIT, no significant recurrence was observed. An octogenarian male, previously treated for tongue cancer with partial tongue resection and radiotherapy, presented with a localized recurrence in the lateral wall of the oropharynx four decades post-initial treatment. Subsequent management involved near-infrared photoimmunotherapy (NIR-PIT), following which no recurrence was detected 16 months after the surgical intervention [23]. Hiromasa Ishihara presented clinical findings on a quintet of individuals afflicted with head and neck squamous cell carcinoma (HNSCC), who were administered seven sessions of near-infrared photoimmunotherapy (NIR-PIT). The patients' responses to the NIR-PIT therapy were anticipated by analyzing variations in serum damage-associated molecular patterns (DAMPs), specifically high mobility group box 1 (HMGB1) and heat shock protein 70 (Hsp70), alongside cytokine and chemokine synthesis, pre- and post-NIR-PIT therapy. Findings indicated that post-treatment serum HMGB1 levels rose in all subjects except for a single case that did not exhibit a clinical improvement, yielding a statistically significant p-value of 0.031 as determined by the Wilcoxon test. Moreover, notable elevations in the chemokines macrophage inflammatory protein-1 alpha (MIP-1α or CCL3) and MIP-1β (CCL4) were observed within the first three days following therapy, with CCL3 reaching a p-value of 0.0036 and CCL4 a p-value of 0.0016, both calculated via the Wilcoxon test [24]. A decreased pretreatment neutrophil-to-lymphocyte ratio (NLR) correlates with enhanced therapeutic efficacy and prolonged survival rates. Elevation of DAMPs and synthesis of cytokines/chemokines were observed within the peripheral blood circulation of affected individuals. Consequently, NIR-PIT therapy emerges as a highly prospective approach for addressing a variety of cancers through precise targeting of neoplastic cells, fibroblasts, and the immune system components. Haruka Yamaguchi's investigation revealed that the salivary gland carcinoma cell lines HSY and A253 exhibited expression of EGFR proteins, as confirmed through immunocytochemical and western blot methodologies. Cells from the HSY and A253 lines, when subjected to EGFRAffibody-IR700Dye conjugate treatment, exhibited an intensification of IR700Dye fluorescence in comparison to untreated samples. EGFR-positive cells subjected to NIR-PIT exhibited signs of cellular disruption and vesicle formation, in contrast to the EGFR-negative cells (MCF7), which remained morphologically intact. During the Alamar Blue cellular viability assay, the HSY and A253 cells, post-treatment with NIR radiation (at 80 J/cm²) alongside the EGFRAffibody-IR700Dye conjugate, sustained diminished cellular viability. In live animal testing, EGFR-positive A253 tumors demonstrated a heightened fluorescence intensity of IR700Dye in comparison to the untreated group. Tumor volume in the NIR-PIT-treated A253 cohort was notably reduced over 43 days, in stark contrast to the untreated and control groups, which experienced swift tumor expansion [25]. The findings collectively confirm that the EGFRAffibody-IR700Dye conjugate demonstrates a high level of specificity in binding to and imaging EGFR-positive tumors. The therapeutic efficacy of Near-Infrared Photoimmunotherapy (NIR-PIT) utilizing the EGFRAffibody-IR700Dye conjugate was established for the treatment of epidermal growth factor receptor (EGFR)-positive salivary gland carcinoma (SGC). Nanami L. Miyazaki et al. The data indicated that RM-1929NIR-PIT achieved a disease control rate ranging from 66.7% to 100% in subjects with unresectable and/or recurrent head and neck squamous cell carcinoma (HNSCC). The comprehensive remission rates exhibited variability, with values spanning from 43.3% to 100%.Mild localized postoperative pain and perioperative edema were the predominant adverse effects documented in patient reports [26]. Initial findings regarding the clinical application of RM-1929NIR-PIT indicate that the treatment is characterized by good tolerance among patients. NIR-PIT represents a novel and promising therapeutic approach for the treatment of head and neck tumors.

3.2. In Breast Cancer

Breast cancer, currently ranked as the second most prevalent form of cancer in terms of new cases globally, is projected to affect approximately 2.3 million individuals. In 2020 alone, an estimated

685,000 fatalities were attributed to this malignancy, with a persistently rising incidence rate observed. Surgical intervention remains the principal therapeutic modality; however, it is accompanied by certain drawbacks, including its invasive nature and concerns regarding cosmesis. To address the intrinsic limitations associated with traditional surgical interventions, it is imperative to devise innovative therapeutic strategies for breast cancer that can ameliorate the deleterious consequences of the disease. Haruka Yamaguchi pioneered the utilization of HER2Affibody-IR700Dye conjugates alongside trastuzumab-IR700Dye conjugates in the therapeutic intervention for breast cancer. The resultant near-infrared photoimmunotherapy (NIR-PIT) combination exhibited marked anticancer efficacy specifically against HER2-positive cellular populations. Trastuzumab demonstrates potent anticancer activity, effectively targeting HER2 low-expressing cells, trastuzumab-resistant cell lines, as well as brain metastases arising from HER2-positive breast cancer cases. The present study constitutes the inaugural report demonstrating the efficacy of the near-infrared photoimmunotherapy (NIR-PIT) approach in combating cancer cells that exhibit resistance to trastuzumab. This finding significantly expands the therapeutic potential of NIR-PIT, offering a novel strategy for the treatment of brain metastases [25]. Haruka validated the therapeutic efficacy and potential of the combined treatment modality through a comprehensive examination of various HER2-positive breast cancer cell lines, including SK-BR3, MDA-MB361, and JIMT1. Susumu Yamashita observed that HER2-positive breast cancer cell lines, after NIR-PIT treatment, exhibited signs of cellular swelling and blister formation in the immediate aftermath of irradiation, culminating in a marked increase in the population of propidium iodide (PI)-positive cells indicative of cell death. Diffuse necrosis was observed in the tumor tissue one day post-irradiation [27]. The findings imply that near-infrared photoimmunotherapy (NIR-PIT) employing trastuzumab-IRDye700DX conjugate (Tra-IR700) elicits a high degree of therapeutic selectivity in HER2-positive breast cancer xenograft models. The utilization of NIR-PIT with Tra-IR700 is anticipated to represent an innovative therapeutic modality for the treatment of HER2-positive malignancies, such as breast cancer. In a comparative investigation encompassing both in vitro and in vivo experimentation, two distinct triple-negative breast cancer (TNBC) cellular models, characterized by moderate and high expression levels of the epidermal growth factor receptor (EGFR), were utilized. These models, MDAMB231 (moderate EGFR) and MDAMB468 (high EGFR) were allocated to diverse treatment cohorts, each receiving varying concentrations of cetuximab (CET)-IR700 conjugate to assess the efficacy of near-infrared photoimmunotherapy (NIR-PIT) as a therapeutic intervention. The findings revealed that, in comparison to the control group, All therapeutic protocols within the NIR-PIT treatment cohort, encompassing single-dose NIR-PIT ($p<0.05$), biphasic NIR-PIT ($p<0.01$), and triphasic NIR-PIT ($p<0.001$), exhibited significant correlations with enhanced tumor regression and improved survival outcomes. The study cohort exhibited statistically significant reductions in tumor growth rates and enhancements in survival outcomes. This investigation established a protocol for enhancing the efficacy of apoptosis-inducing photodynamic therapy (APC) and near-infrared (NIR) photodosing. Findings confirmed the therapeutic efficacy of NIR-Photodynamic Immunotherapy (NIR-PIT) in triple-negative breast cancer (TNBC), irrespective of epidermal growth factor receptor (EGFR) expression levels. Moreover, the study revealed that subjecting the APC dose to fractionation and administering repeated light exposures could significantly enhance patient survival rates [28]. Cui et al. Investigators have recently executed preclinical studies aimed at targeting various transmembrane proteins, including HER2, for Near-Infrared Photoimmunotherapy (NIR-PIT) in the context of breast cancer treatment. The findings indicate that near-infrared photoimmunotherapy (NIR-PIT) demonstrates potential as a novel therapeutic modality for the treatment of breast cancer [29].

3.3. In Ovarian Cancer

Ovarian cancer, classified as a deadly malignant neoplasm, is typified by its refractory nature to early detection, a propensity for relapse, frequent concurrent lymph node involvement, widespread peritoneal metastasis, and a substantial mortality rate. Jiefu Jin and colleagues... Utilizing near-infrared photoimmunotherapy (NIR-PIT), we targeted programmed death-ligand 1 (PD-L1) within

an in situ model of homozygous ovarian cancer. The therapeutic efficacy of Near-Infrared Photoimmunotherapy (NIR-PIT) was initially assessed in vitro using ovarian cancer cell lines and macrophages. Subsequently, an in vivo investigation was conducted within a homozygous in situ ovarian cancer model to further evaluate the treatment's potential. The ovarian cancer model was subsequently subjected to in vivo investigation. The findings indicated that in the context of ovarian cancer, residual tumors and peritoneal metastases were accessible to illumination with near-infrared (NIR) light during surgical procedures. Furthermore, the employment of alternative cancer-specific or TAM-related molecular targets can enhance the efficacy of NIR-PIT in the management of ovarian cancer. Consequently, the utilization of NIR-PIT directed against PDL1 may address a critical therapeutic gap, offering a promising strategy for combination with established treatments to augment therapeutic outcomes in patients with ovarian cancer. Sato Kazuhide and colleagues. Subsequently, the therapeutic efficacy of Near-Infrared Photoimmunotherapy (NIR-PIT) was assessed in a murine model of disseminated peritoneal ovarian cancer. This evaluation involved both in vitro and in vivo experimentation, utilizing a HER2-expressing and luciferase-expressing ovarian cancer cell line, specifically SKOV-luc. In vitro experiments demonstrated that the cytotoxicity induced by near-infrared photoimmunotherapy (NIR-PIT) was positively correlated with the light dose administered. Prolonged illumination stimuli elicited the total eradication of tumor cells within a three-dimensional spheroid model. In the in vivo setting, the efficacy of Near-Infrared Photoimmunotherapy (NIR-PIT) as an antitumor treatment was validated through a marked decrement in both tumor volume and luciferase activity across lateral abdominal and peritoneal mouse models. Specifically, the lateral abdominal model demonstrated a significant reduction in tumor volume at day 10 post-NIR-PIT treatment compared to the control group, with a P-value of 0.0001, indicating statistical significance. Day 4 luciferase activity assessment yielded a statistically significant difference with a P-value of 0.0237; in the peritoneal model, the comparison between the NIR-PIT group and the control group demonstrated efficacy. On the seventh day, the control group exhibited a statistically significant luciferase activity with a p-value of 0.0037. Notably, near-infrared photoimmunotherapy (NIR-PIT) was observed to facilitate efficient cytotoxicity within the HER2-positive experimental model of disseminated peritoneal ovarian cancer [30]. The research team, including Harada Toshiko, validated the practicality of NIR-PIT in a mice model affected by metastatic peritoneal ovarian carcinoma (derived from SHIN3 cells), by conjugating GSA-IR700 with the β-D-galactoside receptor. Findings revealed that the application of multiple NIR-PIT sessions markedly inhibited tumor growth, as indicated by enhanced bioluminescence, demonstrating a statistically significant difference ($p<0.05$) when contrasted with untreated controls, those exposed solely to NIR light, and those treated only with GSA-IR700. Consequently, the repetitive use of NIR-PIT in conjunction with GSA-IR700 conjugation proved to be a potent strategy for tumor inhibition. Hence, the potential of NIR-PIT as an innovative therapeutic approach for the management of ovarian cancer is substantiated [31].

3.4. In Thoracic Cancer

Thoracic cancers, including lung carcinoma, particularly small cell lung carcinoma (SCLC), and malignant pleural mesothelioma (MPM), are notorious for their grim prognoses and the scarcity of truly efficacious treatments. GPR87, a receptor linked to G-proteins, is predominantly found within cancerous cells and scarcely within healthy tissue, making it an attractive target for anticancer therapies. Yasui Hirotoshi's immunohistochemical studies demonstrated that GPR87 is overexpressed in lung tissue and samples excised from MPM surgeries. With a notable 54% of lung cancer patients and all MPM patients presenting with heightened GPR87 expression, the data suggests that targeting this receptor with near-infrared photoimmunotherapy (NIR-PIT) could be a potent treatment approach for these chest malignancies. Evaluation of NIR-PIT's therapeutic potential against such intrathoracic diseases was conducted using a murine model of pleural dissemination, resulting in encouraging results [32]. Utilizing Near-Infrared Photoimmunotherapy (NIR-PIT) within the domain of lung cancer therapy has been observed to yield effective outcomes in tackling several primary lung carcinomas, accomplishing swift tumor destruction through its catalytic action. An innovative

therapeutic technique, characterized by endoscopic manipulation, has been developed to tackle malignant growths, while concurrently stimulating a vigorous immune reaction against tumors, both in proximity and at remote locations. Research outcomes suggest that the application of near-infrared photoimmunotherapy (NIR-PIT), specifically targeting podoplanin (PDPN), could potentially emerge as an unprecedented and efficacious treatment strategy for addressing malignant pleural mesothelioma (MPM) and pulmonary carcinomas [33].

3.5. Application in Digestive System Tumors

Furthermore, the research conducted by Girgis Obaid and colleagues. Explore the crafting of innovative therapeutic modalities for pancreatic ductal adenocarcinoma (PDAC), focusing intently on augmenting therapeutic outcomes through the deployment of meticulously designed near-infrared (NIR) activated photoimmune nanoconstructs (PINs) [34]. Aung Winn initiated research into the therapeutic potential of near-infrared photoimmunotherapy, achieved through the fusion of indocyanine green with antibodies targeting tissue factor, within a rodent model suffering from pancreatic carcinoma. This NIR-PIT intervention significantly curtailed the proliferation of malignant growths, showcasing a considerable decrement in tumor size relative to the untreated cohort, with the greatest differential observed on the 27th day after the onset of treatment. Post-treatment evaluation with hematoxylin-eosin dye revealed patterns of cell necrosis within the tumors, while immunohistochemical analysis detected a diminished count of Ki-67-expressing cells, signaling a decrease in the rate of cellular duplication. The union of 1849-ICG conjugated NIR-PIT therapy is poised to introduce a groundbreaking therapeutic approach for the treatment of pancreatic cancer occurrences marked by TF expression [33].

In the context of the EGFR-expressing hepatocellular carcinoma xenograft in murine models, the therapeutic intervention of near-infrared photoimmunotherapy (NIR-PIT) combined with Cetuximab-IR700 was explored. Results from the vivisectional studies elucidated a notable inhibition of tumor progression, with a stark contrast to the growth trajectory observed in the non-treated cohort. Histological examination post-NIR-PIT therapy unveiled distinct cellular alterations, including cytoplasmic vacuolization and nuclear irregularities, indicative of cancerous cell injury. A subsequent downturn in the Ki-67 labeling index was detected following the NIR-PIT intervention, suggesting a diminished mitotic rate within the carcinoma cells. The findings of this probe affirm the potential of cetuximab-IR700-mediated NIR-PIT as a viable therapeutic modality for targeting EGFR-positive hepatocellular carcinoma [35]. Drawing upon the results garnered from the preceding tests, it is deduced that the employment of near-infrared photoimmunotherapy (NIR-PIT), upon stimulation by light excited in the near-infrared spectrum, facilitates its precise endoscopic delivery through the medium of a fiber-optic disseminator. This positions NIR-PIT as a nascent and promising modality for the management of malignancies within the alimentary canal [36].

3.6. Bladder Cancer

Bladder cancer, a prevalent malignant neoplasm, is classified into two distinct categories based on tumor staging: non-muscle invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC). Despite the existence of various therapeutic interventions, patients suffering from non-muscle-invasive bladder cancer (NMIBC) exhibit a considerable incidence of postoperative relapse. Concurrently, individuals with muscle-invasive bladder cancer (MIBC) face a suboptimal prognosis. Bernhard, Kiss, et al. Following NIR-PIT targeting of CD47, a marked enhancement in phagocytic engulfment of cancer cells was observed, concomitant with a significant deceleration in tumor growth in the treated animal cohort. Moreover, iterative administration of NIR-PIT directed against CD47 led to an additional decrement in tumor progression and resulted in improved survival outcomes. Thus, it is plausible that near-infrared photoimmunotherapy (NIR-PIT) directed against CD47 may selectively promote apoptosis in cancer cells while concurrently mitigating harm to the healthy urinary tract epithelial tissue. The experimental findings indicate that near-infrared

photoimmunotherapy (NIR-PIT) holds potential for the site-specific management of bladder cancer, and may serve as a complementary modality to enhance surgical outcomes [37].

3.7. In Other Tumors

Tadanobu Nagaya's inquiry elucidated that the application of near-infrared photoimmunotherapy (NIR-PIT) drastically curtailed the multiplication of B-cell lymphoma neoplasms, presenting a notable deceleration in the augmentation of tumors when juxtaposed with solely APC-injected intravenous therapy and a control group subjected only to NIR illumination, achieving statistical significance below the $p<0.001$ threshold for both categories of tumors. The administration of a solitary near-infrared photoimmunotherapy (NIR-PIT) session achieved the elimination of over half of the tumors. Notably, the survival period of subjects affected by Daudi and Ramos tumors significantly increased, with the statistical significance level being below $p<0.001$ for the Daudi variant and below $p<0.0001$ for the Ramos type, in contrast with the remaining experimental cohorts. The research suggests that rituximab-IR700, a conjugate of the anti-CD20 antibody, demonstrates exceptional effectiveness when utilized as an antigen-presenting cell (APC) in the context of NIR-PIT aimed at CD20-positive B-cell lymphomas [38].

The protein known as prostate-specific membrane antigen (PSMA) is a promising candidate for therapeutic intervention in prostate cancer, attributed to its excessive expression as a membrane protein in malignant prostate cells. A research investigation was carried out to assess the therapeutic potential of near-infrared photoimmunotherapy (NIR-PIT), employing a human-derived IgG1 monoclonal antibody (mAb) that specifically binds to PSMA, linked to the photosensitizer IR700DX. The exploration into the PC3 lineage of prostate carcinoma cells, known for their expression of PSMA, was conducted meticulously. The research revelations indicated that near-infrared photoimmunotherapy profoundly inhibited neoplastic proliferation (with a significance level below 0.001) and substantially prolonged the lifespan of subjects relative to the untreated cohort (also with a P-value below 0.001). Both therapeutic modalities yielded notable outcomes in curbing the growth of neoplasms ($P<0.001$) and in enhancing longevity ($P<0.0001$), with each therapeutic intervention leading to the resolution of more than two-thirds of the neoplastic formations, as compared to the additional untreated groups. The employment of near-infrared image-guided photoimmunotherapy, in synergy with an anti-PSMA-IR700 human monoclonal antibody conjugate, enabled the seamless transition of benchtop discoveries into real-world clinical practice [39].

4. CHALLENGES AND PERSPECTIVES OF NEAR-INFRARED PHOTOIMMUNOTHERAPY

Photoimmunotherapy utilizing near-infrared light, otherwise known as NIR-PIT, emerges as a pioneering therapeutic technique for combating cancer, holding substantial prospects for its versatility in treating a wide spectrum of cancerous conditions. Merging this groundbreaking modality with conventional cancer treatments has the potential to markedly improve the predictive health outcomes for those afflicted with cancer. The advancements in cutting-edge near-infrared optical conveyance systems, the amalgamation of coherent NIR optical manipulation techniques, and the adoption of instantaneous therapeutic efficacy assessment protocols via real-time surveillance have collectively bolstered the healing possibilities of NIR-PIT within the cancer therapy domain. The latest research revelations on hybrid multicycle dosing magnetic resonance (HMD-MR) techniques open up a broader scope for the deployment of near-infrared photoimmunotherapy in oncology [40]. The exploration of Near-Infrared Photoimmunotherapy (NIR-PIT) has been extensively conducted, examining its efficacy in diverse conditions ranging from oncological to non-oncological, through meticulous research in both experimental in vitro settings and live in vivo animal models. This therapeutic approach has yielded encouraging results, leading to its broad deployment in current

clinical experiments. NIR-PIT has proved its efficacy in eliminating teratomas, a complication in tissue engineering processes, thus obviating the need to reject engineered grafts.

The evident potential of Near-Infrared Photoimmunotherapy (NIR-PIT) in the therapeutic sphere is pronounced, yet recognizing its inherent drawbacks and obstacles remains important. The utilization of near-infrared (NIR) radiation for activation purposes inherently demands the employment of NIR light sources, while the extent and precision of its tissue penetration are intrinsically confined. Subsequent scrutiny is imperative to ascertain the ideal spectrum of light and to delineate the precise parameters for the duration and extent of photic stimulation. Prolonged exposure to light may precipitate deleterious effects on contiguous tissues, affecting vital organs such as the hepatic and renal systems. Complications, ranging from diffused regional swelling, and unintentional decrement in body mass, to a subtle peri-tumoral dermal effusion in select individuals, could emerge, possibly triggering acute therapeutic complications. The exploration of the security aspects, deleterious impacts, and pain-alleviating approaches linked with Near-Infrared Photoimmunotherapy is scant, thus mandating protracted observation intervals and supplementary experimental inquiries.

NIR-PIT has demonstrated remarkable progress in scientific questions and emerged as an applicable candidate for beneficial use in the realm of cancer. This technique establishes itself as a promising approach for cancer therapy through mechanisms such as membrane damage, ICD, SUPR, and so on. Nonetheless, the therapy's entry into clinical practice is in its infancy, and the range of treatable cancers remains limited. Profound exploration into the potential hazards and security aspects of Near-Infrared Photoimmunotherapy (NIR-PIT) is crucial before its adoption into routine medical procedures. Further scholarly pursuits should focus on determining the most effective usage regimen for NIR-PIT, while concurrently examining its cooperative employment with other treatment approaches to enhance therapeutic outcomes.

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