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Laser Photo Chemotherapy: An Alternative Treatment for Cancer

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1. Introduction

The application of quantum electronic devices like lasers and high speed MRI provide the potential for less invasive detection techniques and drastically improved treatment of cancer (Upile et al., 2011). Lasers employ the principle of stimulated photon emission to produce light that markedly differs in quality, depending on the wavelength of the radiation in ultraviolet (UV), infrared (IR) or visible regions of the spectrum (Joffee et al., 1989). In this context, laser fiber optics have been used for minimally invasive access and treatment of inoperable cerebral and head and neck neoplasms as well as tumors in other organs and systems (Feyh et al., 1996; Jager et al., 1996; Vogl et al., 2002a; Vogl et al., 2002b).

For the past 50 years, several laser technologies have been employed in surgical oncology, including CO_2 laser for cutting and coagulating and laser-induced thermal therapy (LITT) for thermal ablation of cancer. Photodynamic therapy (PDT) is an approach which has a wide range of application from acne to wrinkles, bactericidal cleansing, cancer treatment, etc (D'Cruz et al., 2004). In PDT, the absorption of photons by organic compounds can excite orbital electrons and increase kinetic energy levels leading to chemical reactions, but also may include light emission as fluorescence or transfer energy directly to oxygen molecules forming singlet and free radical species (Carmichael et al., 1983; Paiva et al., 1996).

Anthracyline derivatives, such as adriamycin and daunomycin, are the most common anticancer agents that interact with light to elicit fluorescence, membrane photo labeling, laser activation and killing of tumor cells (Andreoni et al., 1991; Nahabedian et al., 1988; Saxton et al., 1996). Studies with these anticancer agents include reports of excited states of these drugs and further generation of radical oxygen species which appear to be wavelength dependent, from 313 to 498nm (Paiva et al., 1996). Some reports have shown that yeast cells were sensitized and killed by adriamycin after irradiation at 365nm, a wavelength that presented no effect in the absence of the drug. Also, cytotoxicity of several anthracycline derivatives are significantly enhanced by continuous wave green light of argon (514nm) or KTP (532nm) laser illumination of different types of cancer, both *in vitro* (Li and Chignell, 1987; Paiva et al., 1996) and *in vivo.*(Nahabedian et al., 1988; Peavy et al., 1992; Soudant et al., 1992; Paiva et al., 1995).

Minton and Ketcham (1965) first described enhanced potentiation of the oncolytic capability of a pulsed ruby laser when combined with cyclophosphamide in a melanoma tumor model in 1965. Although lasers were initially very cumbersome in the operating room, these authors visualized the potential benefits of combined drug and laser tumor ablation. Carmichael et al. (1983) and Li and Chignelli (1987) raised the possibility of using chemotherapeutic drugs to photosensitize tumors since many are chromophoric and absorb light at specific wavelengths of the visible spectrum leading to energy transfer and oxygen species which cause photo-oxidation. Based on such concept, several clinical studies combining chemotherapy with laser therapy were developed in the mid-1990s (Lueder and Goyal, 1996; Murphree et al., 1996).

Previous studies with anthracyclines such as adriamycin and daunomycin have shown that tumor cell peroxidation and membrane photo labeling occur immediately after drug uptake (Myers). Both drugs cause oxidative damage to cardiac tissue even in the absence of light. However, spin label experiments have been reported that show light activation of these drugs induces chemical bonding to many different cell membrane proteins (Li and Chignell, 1987). Anthracyclines initially bind to tumor cell membranes before transport in the nucleus and are considered to be poor type-II photosensitizers, which do not generate significant amounts of singlet oxygen (Andreoni et al., 1993). Nevertheless, these chemotherapy agents are the most tested in hopes of enhancing three distinct anti-cancer effects when combined with visible light: photo toxicity, thermal-toxicity and chemotherapy per se (Saxton et al., 1995).

Recent attempts to reduce anthracycline toxicity led to the development of a variety of anthrapyrazole derivatives including DUP-941 (CI-941), which possess reduced side effects but has been shown to retain clinical efficacy in breast cancer patients (Diwu and Lown, 1994). An unusual property of DUP-941 is that it has an over 100-fold increased photo-oxidation potential compared to anthracyclines as reported by Reszka et al. (1992). Ongoing clinical studies are being conducted to determine the impact that this alternative approach of combining laser and anti-cancer agents may have on the control of disease, survival and quality of life in cancer patients (Paiva et al., 2005b; Paiva et al., 2005c).

In addition to the advantage of photo-activation, several of these light sensitive chemotherapeutic agents have been reported to exhibit enhanced toxicity in tumor cells after photo-thermal-activation (Chung et al., 2003; Graeber et al., 1999; Graeber et al., 1998; Paiva et al., 1995; Saxton et al., 1996). As a result, a potentially useful and less invasive approach for treatment of malignancies is to combine imaging guided interstitial laser surgery with conventional chemotherapy (Paiva et al., 2005b; Saxton et al., 1995). Several FDA approved anti-cancer drugs are highly photosensitive or heat-responsive, including anthracycline derivatives and cisplatin (Paiva et al., 1997; Graeber et al., 1999). This experimental technique broadens the concept of tumor ablation based on thermal denaturation of malignant cells to include anti-cancer drug activation by laser energy (Chung et al., 2000; Diwu and Lown, 1994; Nahabedian et al., 1988).

A major development is already taking place in photo chemotherapy as computer-modeled nanoproducts have proven to be ''intelligently-guided'' by heat sensitization. Nanoshells are optically tunable core/shell nanoparticles that can be fabricated to strongly absorb in the near-infrared (NIR) region where light transmits deeply into tissue (Saxton et al., 1995). Injecting nanoshells systemically will allow enhanced photo thermal ablation of tumor irradiated with the Nd:YAG laser (Feyh et al., 1996; Joffee et al., 1989).

Tumor specificity can be increased by functionalizing the nanoshell surface with tumor-targeting moieties. Moreover, nanoshells can also be made to strongly scatter light and therefore can be used in various imaging modalities such as dark-field microscopy and optical coherence tomography (OCT). After adjustments to the NIR absorbing nanoshells have been finalized, the next step will be to explore image-guided systems in combination with LITT, which will be the ultimate goal of photochemotherapy as a minimally invasive alternative therapy for cancer.

In this article, the authors review the literature that supports combining anti-cancer drugs and laser for cancer therapy. These studies suggest that photo chemotherapy with currently approved drugs and lasers may soon become an attractive alternative for cancer treatment. PDT studies were not in the scope of this work, as photodynamic application in clinical oncology is already a well-established subspecialty in laser technology.

2. Laser photo-thermal therapy for cancer

The pathway towards the realization of optical solid-state lasers was gradual and slow. After Einstein's paper on absorption and stimulated emission of light in 1917 it took until 1960 for the first solid state laser device to see the light. Laser systems are widely spread in the field of medicine (Upile et al., 2011). The applications are divided into therapeutical and diagnostic applications. The main field however, is therapeutical procedures. Depending on the indication lasers were used for removing and cutting of smooth and hard tissue or for coagulation. A relative new procedure is image guided laser thermal ablation of solid tumors. As early as 1964, Goldman and Wilson reported clinical results on the treatment of basal cell epithelioma using laser radiation.

In 1964 experimental investigations on the potential of lasers to destroy malignant tumors began with studies by using high energy pulsed laser radiation for treatment of multiple intra-abdominal tumor implants in experimental animals (Minton and Ketcham, 1964). Richey and Dixon (1981) investigated a similar treatment of gastric polyps by endoscopic application of lasers, a similar technique used by Sasako et al. (1982) for treating gastric cancers with the Nd:YAG laser. Hofstetter and Frank (1979) previously reported the successful use of laser endoscopy for clinical treatment of bladder tumors. Shapshay and Strong (1982), Brunetaud et al. (1981), and Carpenter et al. (1977) presented in separated publications, that successful management of tracheal lesions could be obtained using the Nd:YAG laser. Fleischer et al. (1982) reported tumor palliation in a series of 14 patients with end stage carcinoma of the esophagus treated with the Nd: Y AG laser.

The Nd:YAG laser emits luminous energy in the near infrared portion of the visible spectrum at 1064nm and is poorly absorbed by hemoglobin, melanin and water, which leads to scattering of the laser beam with deep penetration into tissues (Feyh et al., 1996; Joffee et al., 1989; Mueller-Lisse et al., 1998; Sturesson and Andersson-Engels, 1996). Transmitting laser energy directly through a fiberoptic cables allows the surgeon to deliver more effective localized treatment, minimizing undesired tissue damage to adjacent structures, which is the main advantage of this adjuvant therapy for malignancies (Castro et al., 1994; Feyh et al., 1996; Joffee et al., 1989; Paiva et al., 1998a). The Nd:YAG laser is widely used in endoscopic and open surgery due to its photo thermal ability to coagulate, cut, vaporize and ablate tissue (Castro et al., 1994; Joffee et al., 1989; Paiva et al., 1998a). Thus, the Nd:YAG is a unique versatile tool for localized thermal ablation of tumors.

The minimally invasive methods for tumor ablation currently available are using thermal probes, infrared thermography, and histological studies, which are reliable but have limited clinical usefulness (Stafford et al., 2010). Since the mid-1970s, interstitial placement of laser fiber optics has been applied successfully in large subcutaneous metastasis. In 1985, Svaasand developed some preliminary optical dosimetry for interstitial phototherapy of malignant tumors. About the same time Matthewson et al. (1987) investigated interstitial use of the Nd:YAG laser (1-2W) for hepatic hyperthermia to produce areas of thermal necrosis up to 16mm in the normal rat liver, and to eradicate induced rat colon tumors and implanted fibrosarcomas. Hashimoto et al. (1986) applied 5-15 W of Nd: YAG laser power with a modified diffuser fiber tip to treat liver tumors with evidence of reduction of tumor size. Godlewski et al. (1988) used high Nd: YAG powers (100 W), with one second duration to produce areas of vaporization and necrosis of 16-22 mm in porcine liver at great speed. However, the high power density at the distal end of the fiber optics resulted in frequent tip damage, burning, non-uniform distribution of laser energy, and poorly reproducible tissue effects. In 1985, Daikuzono and Joffe introduced synthetic sapphire probes that have high melting points (2020-2050°C), greater tensile strength, and a uniform pattern of laser beam delivery from the lateral surface of the probe. These probes allowed testing of Nd:YAG laser-induced hyperthermia in a dog mode1, and further developed a computer-controlled Nd:YAG system for interstitial local hyperthermia.

To increase the area of necrosis that could be produced and still use one laser as the energy source, Steger et al. (1989) used fiber optic coupling systems to increase the number of fibers that could be inserted. This concept, while attractive, has proved difficult to achieve in practice. Nevertheless, the same author introduced the term interstitial laser hyperthermia in cancer treatment, which later on established itself as laser-induced thermal therapy, or LITT. Gatenby et al (1987) used computerized tomography (CT)-guided laser therapy for treatment of resistant human tumors in ten patients with favorable results. Steger et al. (1992) used ultrasound imaging to monitor the percutaneous interstitial Nd:YAG laser treatment of ten patients with liver tumors and found ultrasound imaging to be a sensitive monitoring technique of thermal necrosis.

Computed tomography scanning demonstrates poor sensitivity to early tissue changes after laser exposure because of low soft-tissue contrast resolution. Using image-guided systems as CT, and ultrasound. Castro et al. (1994), at the University of California, in Los Angeles (UCLA) , made significant contributions to define Nd:YAG laser doses that could be safely translated into effective clinical application. Blackwell et al. (1993) first reported results of a pilot study testing interstitial laser ablation of neck tumors guided by ultrasound. The method later evolved into minimally invasive MRI-guided treatments as described by Pushek et al. (1995). Sinha et al. (1997) established temperatura monitoring system for thermal-ablative procedures using a software system that correlated tissue changes with MRI imaging.

MRI is a non-invasive and extremely sensitive diagnostic imaging system, used to locate and guide biopsies of deep and difficult tumors and to access target tissues using needles with extremely low magnetic susceptibilities (Kahn et al., 2008; Pushek et al., 1995). MRI has the potential to become a three-dimensional, real-time, video imaging technique that can provide accurate and detailed anatomic information during laser surgery (Kahn et al., 2008; Vogl et al., 2002b). Important advances in clinical applications of imaging-guided laser ablative procedures were developed in the mid 1990s by different groups in Germany.

Particularly in MR-guided LITT liver tumors, Vogl et al. (1997) showed local tumor control between 96.3% and 98.8% after 3 months and between 95.6% and 98.8% after 6 months. No local recurrence was observed later than 6 months after LITT. Although the intention for LITT was originally palliative, its favorable survival rates compared with those obtained with surgical resection of liver metastases on the basis of analyses of large surgical series with lower complication rates, are encouraging (Vogl et al., 2002a; Vogl et al., 2002b; Vogl et al., 2009).

The recent development of software programs for mathematical models of imaging-guided LITT should lead to more effective tumor palliation with laser therapy as an alternative to surgery (Mohammed and Verhey, 2005). In sum, image-guided ablation of tumors is assuming an increasingly important role in many oncology services as a minimally invasive alternative to conventional surgical interventions for patients who are not good candidates for surgery. LITT is now a multi-specialty procedure used for treatment of inoperable tumors of the brain, head and neck, breast, liver, prostate and colon, as a minimally invasive and low cost cancer therapy (Castro et al., 1994; Chapman, 1998; Mueller-Lisse et al., 1998; Paiva et al., 1998a; Schulze et al. 2002; Vogl et al., 1997; Vogl et al., 2002a; Vogl et al., 2002b; Mack et al., 2004; Marga et al., 2011). Further improvement will be possible by combining LITT_with novel systemic therapy such as targeting agents, gene therapy, or nano-designed thermo-sensitive drugs (Kanekal et al., 2009).

3. Photo-chemical and photo-thermal activation of anti-cancer drugs

Tissue interactions with laser irradiation are typically classified as photochemical, photomechanical, and photo thermal (Feyh et al., 1996; Joffee et al., 1989). Photochemical effects depend on the absorption of light to initiate chemical species in photodynamic therapy (PDT). It is associated with low fluency rates that do not produce a significant temperature increase in the treated tissue, but do not interact with a natural or exogenous photosensitizer to produce the desired reaction. Although we will discuss photochemical effects of laser at length, PDT is not in the scope of this chapter for simplicity. Photomechanical responses occur during applications of extremely high fluency rates (greater than 10^8 W/cm^2 and short laser pulses 10^{-6} sec. or less), which produces shockwaves and plasmas. Such effects occur, for example, when a laser operates in a Q-switch mode.

Photo chemotherapy with lasers is an alternative therapy which consists of using a monochromatic light delivered via external irradiation or via interstitial fiber optics to enhance the ``killing`` threshold in tumors containing light and/or heat -sensitive anti-cancer agents (Saxton et al., 1995). The development of photoactivatable pro-drugs of platinum-based antitumor agents is aimed at increasing the selectivity and thereby lowering toxicity of this important class of antitumor drugs (Bednarski, 2007; Farrer et al., 2010). Hence, laser chemotherapy explores two distinct mechanism of antitumor action: (1-) direct toxic effect, and (2-) additional photochemical and/or photo thermal toxicity (Bednarski, 2007; Crescenzi et al., 2004; Eshraghi et al., 1997; Mackay et al., 2007).

These drugs may be injected intravenously at concentrations lower than normal chemotherapeutic levels, or at higher intratumor doses reducing systemic toxicity while enhancing local tumoricidal effects by laser photoactivation in situ (Nahabedian et al., 1988; Paiva et al., 1998c). Other anthracyclines have also been identified that have greater photosensitization potential than daunomyucin (Diwu and Lown, 1994). With all the supporting evidence of translational studies, photochemotherapy has been established as an

alternative treatment for retinoblastoma (Peterson et al., 2011). Most of these studies were conducted in children where there has been a few standardized clinical protocols, in particular for unilateral retinoblastoma (Leng et al., 2010; Mallipatna et al., 2009; Gallie et al., 1996; Lueder and Goyal, 1996; Murphree et al., 1996; Saxton et al., 1996

The first reports of DUP-941 as an intratumor sensitizing drug for phototherapy in a subcutaneous squamous cell carcinoma (SCCA) transplant model in nude mice were published in 1995 (Paiva et al., 1995). This experimental treatment showed intralesional injections at 60µg DUP-941 per gram of tumor led to stasis but no regression. LITT administered via fiber optics at low energy levels (continuous green light, 532nm, power density = 13.4 J/cm^2) also resulted in tumor recurrence in over 80% of the animals. However, combined intratumor DUP-941 and LITT at the same dose levels of drug and laser energy produced tumor eradication in over 90% of treated animals with no recurrence detected during a 12-week follow-up period. This was the first effort in the literature to explore the concept of local injection of anti-cancer drug combined with laser interstitial therapy for cancer treatment. Additional testing in a larger group of animals in Germany by Graeber et al. (1998) confirmed these results, which provide strong preclinical evidence in support of the hypothesis that photo chemotherapy may be an alternative treatment for human tumors. Similar LITT studies have followed with a translational experimental model combining intratumor cisplatin with Nd:YAG laser for thermal ablation of recurrent and advanced head and neck cancer (Paiva et al., 1998b; Graeber et al., 1999).

Despite important advances in current therapy with surgery, radiation, and chemotherapy, nearly one half of all head and neck cancer patients will develop persistent or recurrent disease (Adelstein, 1998; Argiris et al., 2010; Bonner et al., 2006; Correa and Burkey, 1999; Weisman and Robbins, 1998). Head and neck tumors are an excellent disease model for testing intratumor chemotherapy and laser because of their accessibility for surgery and their loco-regional biological behavior (Paiva et al., 1997). The laser energy can be delivered via interstitial fiber optics using drugs activated by photo-chemical and photo-thermal energy as a potential less invasive treatment alternative for cancer (Paiva et al., 2005c; Paiva et al., 1997; Graeber et al., 1999). Moreover, there has been no generally accepted standard of care for recurrent head and neck cancer (Goodwin et al., 2000; D'Cruz et al., 2004; Arnold et al., 2004; Fury et al., 2011). At UCLA, Phase I and II clinical trials have been conducted using LITT in a stepwise fashion to palliate patients with advanced and recurrent head and neck tumors as an alternative to more radical and at times disabling surgery (Castro et al., 1994; Paiva et al., 1998a; Paiva et al.; 2002a).

4. The rationale for cisplatin and laser thermal-therapy for cancer

Platinum-based compounds were first synthesized in the nineteenth century but their clinical use against cancer did not start until the 1970s (Higby et al., 1974). Cisplatin [(*SP*-4-2)-diamminedichloroplatinum] was the first of the platinum drugs to be approved for the treatment of both ovarian and testicular cancer in 1978 and is also administered for many other types of solid tumors. Second-generation platinum derivative carboplatin [*cis*-diammine (cyclobutane-1,1-dicarboxylate-*O*,*O*_)platinum(II)] differs from cisplatin in the substitution of two chlorides by a 1,1-cyclobutane dicarboxylate group. Its efficacy in the treatment of the above malignancies is equal to that of cisplatin, and its toxicity profile is more favorable and was approved in March 1989 for treatment of ovarian cancer (Ozols et al., 2003). Thus, carboplatin has often been used in place of cisplatin (Syrigos et al., 2010;

Gkiozos et al., 2007). Oxaliplatin [[(1*R*,2*R*)-cyclohexane-1,2-diamine](ethanedioate-*O*,*O*_)platinum(II)] is a third generation platinum compound approved in 2002 (Charalabopoulos et al., 2002). Oxaliplatin is widely used for the treatment of metastatic colorectal cancer and a variety of other malignancies, such as breast cancer, melanoma, non-Hodgkin lymphoma, and head and neck cancer (Makrilia et al., 2010). The other names for cisplatin are DDP, cisplatinum, and cis-diamminedichloridoplatinum(II), or CDDP. Common adverse events are myelotoxicity, nausea, vomiting, diarrhea, paresthesia, and dysesthesias (Makrilia et al., 2010).

The mechanism of anticancer activity of cisplatin is by forming a platinum complex inside of a cell which binds to DNA and cross-links DNA. Consequently, crossed-linked DNA causes the cell to undergo apoptosis, or systematic cell death. Cross-linking ensues apoptosis by damaging the DNA so that the repair mechanisms for DNA are activated, and once the repair mechanisms are activated and the cells are found to not be salvageable, the death of those cells is triggered instead. Clearly, the use of platinum derivatives is essential in the fight against cancer, and currently it is the most commonly used chemotherapy drug in the United States (Seiwart et al., 2007). However, the toxic side effects must be attenuated to reap the maximum benefits, which is why other uses are devised exploring distinct synergistic effects when combining cisplatin with a regimen of other anti-cancer drugs, radiotherapy, whole body hyperthermia, and more recently biologic therapy (Amichetti et al., 1993; Goodwin, 2000; Bonner et al., 2006; Seiwart et al., 2007; Fury et al. 2010).

Whole body hyperthermia has been studied clinically for nearly two decades with respect to cancer treatment and has been shown to enhance tumoricidal effects of irradiation as well as chemotherapy with adriamycin (doxorubicin) and cisplatin (Amichetti et al., 1979; Hahn, 1979; Baba et al., 1989; Storm et al. 1989; Ohno et al., 1994; Engin, 1996; Cezamar et al., 2001; Arancia et al., 2001; Hahn and Shiu, 1983; Noel et al., 2003). In these studies, near maximum effects were observed when both modalities (i.e., hyperthermia and chemotherapeutic agents) were administered simultaneously (Hahn, 1979; Teicher and Herman, 1992). At temperature levels above 43°C, heat also appears to reverse acquired resistance to cisplatin (Hahn, 1979; Cezamar et al., 2001). In particular, hyperthermia enhances the activity of cisplatin by potentiating tumoricidal effects progressively as intra-tumor temperature is elevated to 43°C resulting in synergistic lethal effects for cancer cells (Ohno et al., 1994; Engin, 1996). Thermo-chemotherapy using systemic fever-range (40 C^o) temperature for long durations (4-6 h) has better or equal anti-cancer efficacy compared to maximally-tolerated systemic temperatures (41.5 C^o–42 C^o), and generally results in less toxicity (Bull et al., 2008a).

Bull et al. (2008a) determined the maximally tolerated dose (MTD) of cisplatin administrated within a regimen of fever-range whole body thermal therapy to be 60mg/m^2. Since hyperthermia has the potential to interfere with many mechanisms that cause cisplatin resistance, it may also be a suitable modality to interfere with acquired resistance (Oldenburg et al., 1994; Bull et al., 2008a). Apparently, the mechanisms responsible for hyperthermic cell killing and hyperthermic drug sensitization must, in part, be the same (Hettinga et al., 1995). Heat has been shown to cause denaturation of cellular proteins. This leads to an increase in protein mass of nuclei isolated from heated cells. Under several conditions, including thermo tolerance, a good correlation has been found between the extent and duration of this ``nuclear protein aggregation`` and thermal cell rilling (Hettinga et al., 1995). This nuclear protein aggregation may also be one of the major mechanisms

responsible for thermal potentiation of killing by a number of drugs, which is by hampering repair of drug-induced DNA damage (Hettinga et al. 1995).

Timing of chemotherapy, with respect to potentiation by heat, and of two drugs relative to each other, is critical in determining antitumor efficacy, toxicity, and survival (Bull et al., 2008b; Teischer and Herman, 1992). Significant sequence-mediated differences in antitumor response demonstrated that when cisplatin is administered with gemcitabine an optimization of the administration schedule of multidrug chemotherapy regimens may also prove to be important. Therefore, preclinical optimization of the timing of chemotherapy drugs relative to each other, and drugs relative to heat, in multi-agent thermo chemotherapy regimens could significantly increase tumor response while minimizing toxicity.

Refaely et al. (2001) studied the results of thermo chemotherapy with cisplatin in stage IVa patients diagnosed with thymic malignancies. They found a relatively high 3-year and 5-year survival rates of 70% and 55% for the entire study population, and 90% and 70% for the thymoma patients. These results are comparable, and apparently higher than that reported in other series (Yellin et al., 2001). While it is important to recognize that whole body thermal therapy can enhance some of the toxicities associated with other treatments, the synergy of hyperthermia with several chemotherapy agents means that lower doses can be used, resulting in less toxicity. Among the collateral effects that cisplatin can cause, we find nausea, both acute, and chronic renal toxicity as well as long-lasting neuropathy. These toxicities are acute and treatable (McWhinney et al., 2009).

There are three proposed explanations for the synergism between hyperthermia and cisplatinum: (1) an increase level of drugs within cells; (2) significant enhancement of the DNA cross-linking effect of the drugs; and (3) heat-induced inhibition of DNA repair (Refaely et al, 2001). Evidence indicates that heat induction leads to ultrastructural changes in cell membranes resulting in altered cellular metabolism and increased susceptibility to drug toxicity (Arancia et al., 1989; Hahn and Shiu, 1983). Higher intracellular uptake of CDDP induced by heat also enhances cytotoxicity in proliferating cancer cells and stimulates protein kinase-mediated pathway to tumor apoptosis (Noel et al., 2003).

Drug resistant human carcinoma cells also exhibit increased CDDP uptake and cytotoxicity in the setting of hyperthermia (Flood et al., 1999). In addition, combined CDDP and hyperthermia is effective in the eradication of hypoxic tumor cells which may be resistant to single modality treatment with either radiation or chemotherapy alone (Storm, 1989). The oncogenic potential of CDDP is markedly enhanced by hyperthermia compared to drug treatment alone (Zanke et al., 1996; Beketic-Oreskovic et al., 1997). Studies of CDDP at the molecular level have shown that hyperthermia induces CDDP to bind to DNA forming more DNA adducts, contributes to delayed tumor growth, and amplifies inter-strand crosslinking (Storm et al., 1989; Hettinga et al. 1996; Los et al., 1994; Los et al., 1993). Altogether, the exact biological mechanism of the synergistic effect of combined cisplatin and heat remains unclear (Bednarski et al, 2007; Los et al., 1993).

An initial report by Nahabedian et al. (1988) on photochemotherapy using cisplatin and laser (wavelength 688nm) showed that laser treatment was enhancement by systemic chemotherapy in murine tumors, and was the first *in vivo* evidence of cisplatin-photo activation by visible light. More recently, the development of photoactivatable prodrugs of platinum-based antitumor agents is aimed at increasing the selectivity and thereby lowering toxicity of this important class of antitumor drugs (Bednarski, 2007; Crescenzi et al., 2004; Mackay et al., 2007; Cubo et al, 2010). Cisplatin forms mainly intrastrand cis-diguanine

cross-links on DNA between neighboring nucleotides, whereas photoactivated complex-1 rapidly forms unusual trans azido/guanine, and then trans diguanine Pt(II) adducts, which are probably mainly intrastrand cross-links between two guanines separated by a third base. DNA interstrand and DNA-protein cross-links were also detected. Importantly, DNA repair synthesis on plasmid DNA platinated by photoactivated-1 was markedly lower than for cisplatin or its isomer transplatin (an inactive complex). Single-cell electrophoresis experiments also demonstrated that the DNA damage is different from that induced by cisplatin or transplatin. Cell death is not solely dependent on activation of the caspase 3 pathway and, in contrast to cisplatin, p53 protein did not accumulate in cells after photosensitization of photoactivated complex-1. The trans diazido Pt(IV) complex-1 therefore has remarkable properties and is a candidate for use in photoactivated cancer chemotherapy (Cubo et al., 2010). Even though there was a lack of basic science evidence supporting photochemotherapy with cisplatin in the beguining of the eighties, a wealth of clinical investigations followed testing this experimental treatment for cancer.

5. Clinical relevance of laser and cisplatin in photo chemotherapy

Photochemotherapy (PCT) uses Federal Drug Administration (FDA) approved chemotherapeutic drugs which are first injected into to tumors, thus reducing systemic effects. The sensitized tumor is then activated either by photo oxidation and/or by photo thermal levels of energies using a monochromatic laser light which is delivered via external and/or interstitial fiber optics to enhance the ``killing`` threshold (Saxton et al., 1995). Head and neck cancers are accessible for surgery and have a well documented loco-regional biological behavior. These tumors can therefore serve as an ideal model to test photochemotherapy, as this approach is a possible alternative for less invasive treatment for cancer.

Local recurrence in head and neck cancer is thought to be caused, in many cases, by residual disease and/or contamination of the surgical field during resection. Using an animal tumor model to investigate local recurrence, Maker et al. (1995) observed that Nd:YAG contact laser ablation provided about 50% improvement in the control of local disease in vivo ($p< 0.05$) compared to animals treated with a scalpel. Pilot studies have demonstrated that Nd:YAG (1064 nm) laser induced thermal therapy may also play a role in pain control and allow continued nutritional support for patients with advanced or recurrent head and neck tumors (Castro et al., 1995a; Castro et al., 1994; Jager et al., 1996) Through repeated laser endoscopy, the need for a nasogastric or gastrostomy tube has been avoided as well (Jager et al., 1996; Mitty et al., 1996). Several studies report successful relief of malignant dysphagia and improvement in the quality of life with endoscopic Nd:YAG laser treatment (Karlin et al., 1987; Mitty et al., 1996; Sawant and Moghissi, 1994).

Although LITT procedures are safe, feasible, and can extend survival, margin recurrence is seen in many cases, particularly in advanced obstructing cancers of the gastrointestinal tract or bronchial tree (Castro et al., 1995a; Feyh et al., 1996; Joffee et al., 1989; Mueller-Lisse et al., 1998). In order to improve local tumor recurrence after laser treatment, Firusian (1988) was the first to propose combining Nd:YAG therapy with systemic chemotherapy to improve the final outcome in the palliation of esophageal cancer. The author reported that 13 patients with stenotic upper gastrointestinal cancers treated by endoscopic recanalization with laser ablation and systemic cisplatin in combination with other anticancer drugs responded more favorably compared to laser alone as a palliative approach for advanced malignant disease.

In most of the 13 patients, combined therapy led to immediate patency of the upper alimentary tract and 8 months median survival in the cohort studied. In this study it was also found that local laser thermal effects were enhanced by systemic chemotherapy leading to additional ablation of malignant cells down to 7-8mm depth compared to 4mm for laser treatment alone. Thus, it was concluded that combined drug and laser therapy was more effective in preventing rapid cell proliferation at the tumor margins (Firusian, 1988). The author also compared different anti-cancer agents combined with LITT ablation for inoperable esophageal cancer and reported that cisplatin (CDDP) was more effective than anthracyclines or cyclophosphamide when combined with Nd:YAG laser. However, other studies done in children with retinoblastoma found that Adriamycin derivatives were more cytotoxic in tumors after laser photo-thermal activation (Andreoni et al., 1991; Gallie et al., 1996; Lippert et al., 2004; Lueder and Goyal, 1996; Murphree et al., 1996). From a historical perspective, initial work on chemotherapy and lasers was reported in clinical models investigating combined palliative therapy for inoperable esophageal cancers. Such reports were produced in Germany (Semler et al., 1985), who noticed significant improvement in quality of life in 21 of 24 patients with advanced gastrointestinal tumors treated by systemic chemotherapy administered before intraluminal endoscopic Nd:YAG laser thermal ablation. Mache et al. (1986) also reported on the survival benefits of this alternative combined treatment for palliation of advanced upper gastrointestinal tumors. In a randomized clinical trial, Mason et al. (1996) confirmed that patients with esophageal cancer presented a significant reduction in need for additional laser therapy to maintain swallowing when adjunctive chemotherapy was given before laser treatments. Expanding the same concept, Vogl et al. (2009) have recently proposed a combination of chemoembolization and LITT for liver tumors with promising results. An additional boost for laser thermal therapy has also been reported, when associating systemic cycles using IL-2 human cytokines for palliation of metastatic renal cell carcinoma to the head and neck (Paiva et al., 2007).

Clinical experience with this form of combined therapy for head and neck SCCA was first reported on eight patients with recurrent tumors who enrolled in the first study conducted in the United States testing systemic chemotherapy (CDDP at 80mg/M^2) followed 24 hours later by palliative Nd:YAG laser thermal ablation (Paiva et al., 2000). Four of the 8 patients treated in this manner remained alive after a median follow up of 12 months. A total of twelve tumor sites were treated, and complete responses were seen in the following anatomic locations: oral cavity (n=3), oropharynx (n=1), hypopharynx (n=1), and maxillary sinus (n=1). The median survival for these patients was 9.5 months. The adverse effects of treatment included mild alopecia in a 82 year-old female, and a bout of gastrointestinal infection in another patient (Paiva et al., 2000). A total of 21 patients were treated on this study that showed minimal toxicity of the combined treatment. However, the therapeutic benefit could not be demonstrated because of the variability of the tumor sites in the head and neck that were analyzed (Paiva et al., 2005a). One of the patients treated in this series presented with a recurrent SCCA of the neck after having previously undergone a reconstructive free flap transfer (Joo et al., 2009). The patient underwent 6 concurrent treatment sessions using the protocol mentioned above and demonstrated an unusually long period of survival (i.e., over 5 years). The remarkable survival of this patient suggests that the combination of LITT and chemotherapy warrants further investigation as an alternative treatment for patients with recurrent head and neck cancer. Studies have shown that even more effective eradication of head and neck cancer is possible by combining LITT

with local, intratumor injections of CDDP (Clayman et al., 1999). Currently, cisplatin or cis-diamminedichloroplatinum (CDDP) are the most commonly used chemotherapeutic agents for head and neck cancer (Argiris et al., 2010; Bonner et al., 2006; Forastiere et al., 2006). technology.

6. Intratumor injections of chemotherapy and laser for effective local tumor control

Initial experimental studies combining intratumor injections of cisplatin followed by local hyperthermia were carried out by Kitamura et al. (1992) in a melanoma model. The authors demonstrated that the combined treatment led to 6-fold decreased tumor growth rate of melanoma and improved prognosis without nephrotoxicity or the promotion of hematogenic metastasis. Also, intratumor administration of cisplatin led to animal weight gain in this study, while mice treated with systemic drug had a significant weight loss or absence of weight gain (Kitamura et al., 1992).

In the mid-1990´s several studies explored local adjunct chemotherapy to eliminate marginal tumor regrowth and improve final outcomes after surgery and radiation These studies had a strong rationale based on two reports by authors Theon et al. (1994) and Begg et al. (1994), who proposed adjunct local chemotherapy combined with tumor resection as a more effective approach for cancer treatment. The local chemotherapy proposed was based on a therapeutic implant of cisplatin in a gel vehicle (CDDP/gel) which consisted of purified bovine collagen (a protein carrier), cisplatin and a vaso-constrictor, epinephrine (Deurloo et al., 1991). The therapeutic implant provides sustained release of drug in tumors and greatly reduces systemic toxicity (Krag et al., 1990). Recent studies with human SCCA transplant models combining intratumor chemotherapy with LITT encourages further development of this novel combined therapy to successfully eradicate marginal disease for treatment of recurrent head and neck cancer (Chung et al., 2003).

The rationale for combined treatment is that during LITT, high photo thermal laser energy levels are delivered to the area of maximum obstruction in the tumor core, inducing irreversible coagulative changes and lower levels at the tumor margin. Less energy is delivered to the margins because of higher risk of organ perforation or damage to neighboring tissues (Paiva et al., 1997). LITT debulking procedures causes boiling of tissue water and subsequent irreversible thermal damage, which will ultimately lead to photo-evaporation at the tumor core (≥100 ^{o}C) (Chapman, 1998; Hallddorsson and Langerholc, 1978; Marchesini et al., 1985; Morrison et al., 1998). Local recurrence after LITT is related to residual disease due to reversible cellular thermal damage on the margins treated with subtherapeutic energy levels (40-60^{o}C) in head and neck and prostate tumor ablation (Anzai et al., 1991; Marchesini et al., 1985). Toxicity enhancement of cisplatin at these temperatures (40-60^{o}C) would promote optimal eradication of cancer cells at the tumor margins. Under such rationale, enhanced laser therapy by adjuvant local chemotherapy using CDDP/gel in the region of subtherapeutic energy levels was first demonstrated in an experimental model by Paiva et al. (1997).

Using authographic imaging method, Kanekal et al. (1995) tested cisplatin radiotracer in suspension (^{195m}Pt-CDDP, 4mg/ml) and gel implant form (^{195m}Pt-CDDP/gel, 4mg/ml) to compare tumor retention in 600mm^{3} subcutaneous tumors in experimental murine model. Intratumor CDDP/gel provided a uniform drug concentration at the margins of the tumor

at 4 hours, and 80% drug retention in the tumor as opposed to rapid systemic washout of ^{195m}Pt-CDDP in suspension after intratumor administration. Higher intratumor CDDP levels can allow enhanced direct toxicity as well as a synergistic interaction with laser hyperthermia to further promote cisplatin cytotoxicity (Begg et al., 1994; Graeber et al., 1999; Theon et al., 1994). This hypothesis was tested in multiple studies in which intra-tumor CDDP/gel injections were combined with LITT for enhanced therapy in the tumor margins and further improvement in cancer treatment. This body of translational work provided the groundwork for clinical application of CDDP/gel and LITT for recurrent head and neck cancer (Paiva et al., 2005b). The CDDP/gel dose was based in phase II-III studies where 2.0 mg CDDP/cm^3 tumor was determined to be tolerable, contributed to tumor responses, and provided volume dosing to adequately infiltrate tumor masses. Using this vehicle, 1 mL of CDDP/gel delivers 2 mg of CDDP (Burris et al., 1998; Castro et al., 2003). In one study, eight patients were treated using the CDDP/gel implant and laser combination (oral *n=1;* neck *n=3;* skin *n=2;* maxillary sinus *n=1;* breast *n=1)* where the end point was to study drug toxicity (Bublik et al., 2010). None of the patients experienced toxicity at the levels of laser (2,200J/cm^2) and drug (2mg/CDDP per cm^3 of tumor) tested. However, additional studies are needed to guarantee the safety of combining both treatment modalities. Other studies have confirmed that intratumor injection of cisplatin at 2mg/ml is safe in well-established clinical protocols exploring electro-chemo-poration treatment for skin cancer (Sersa et al., 2000a; Sersa et al., 2000b).

A more recent study by Kanekal et al. (2009) showed that intratumor injections of CDDP in solution washed out after 5 minutes, which shows that combined treatment with LITT could be performed as a one-step procedure in the operating room. This would obviate the need for waiting between tumor injection and laser treatment (typically 4 to 48 hours), making the treatment protocol more efficient and streamlined for patients. Probably the most relevant clinical investigation testing intratumor injection of chemotherapy combined with laser thermal therapy was published by Wang et al. (2001) who reported 100% complete responses in 33 patients with T1-2 esophageal squamous cell carcinoma. In this work intratumor injection of bleomycin was combined with LITT for esophageal tumors and followed for an average 29 months. The combined minimally invasive procedure proposed has a strong translational potential as a cost effective alternative treatment not only for head and neck but for other accessible inoperable primary and/or recurrent tumors of the chest wall, breast, liver, prostate and colon (Castro et al., 1994; Chapman, 1998; Mueller-Lisse et al., 1998; Paiva et al., 1998a; Schulze et al., 2002; Vogl et al., 2002a; Vogl et al., 1997; Stafford et al., 2010; Sercarz et al., 2010).

7. Future development

The next phase of the experimental model for intratumor injections of CDDP followed by LITT will be to introduce the concept of "vascular collapse" potentiating high dose chemotherapy and localized hyperthermia. Peralta et al. (2010) et al. recently described massive thermal injury to arteries and veins resulting in vascular collapse due to high energy density using the Nd:YAG laser powered at 30-45W for treatment of severe twin-twin transfusion syndrome. This is the same energy level used by our group for head and neck thermal ablation (2,200-3,300 J/cm^2) of cancer (Bublik et al., 2006; Sercarz et al., 2010). In theory, the peripheral vascular collapse of arteries and veins produced by LITT will isolate blood flow to and from the tumor, thereby impeding drug (CDDP) washout to the

rest of the body. Consequently, high cisplatin concentration in the tumor will potentiate the cytotoxic synergistic combination of drug and heat, and promote more effective treatment. Potentially, intratumor injections of cisplatin may be increased up to 40mg as recently reported by Celikoglu et al. (2006) in a clinical trial testing local chemotherapy (CDDP/sol) and radiation for inoperable bronchogenic tumor, where no adverse effects were observed. The vascular collapse will avoid systemic diffusion of cisplatin and allow us to attain a very high concentration of CPPD in the tumor margins as first suggested by Sakurai et al., in 1996. High doses of CDDP/sol will significantly improve the combined treatment proposed (Kanekal et al., 2009).

Further progress in laser chemotherapy may be an outgrowth of the current excitement surrounding nanoscience and the promise of new nanoscale applications in cancer diagnostics and therapy. Because of their strongly resonant light-absorbing and light-scattering properties that depend on shape, noble metal nanoparticles provide a new and powerful tool for innovative light-based approaches. Nanoshells are spherical, dielectric core, gold shell nanoparticles that have been central to the development of photo thermal cancer therapy and diagnostics for the past several years. By manipulating nanoparticle shape, researchers can tune the optical resonance of nanoshells to any wavelength of interest (Lal et al., 2008).

Nanoshells are optically tunable core/shell nanoparticles that can be fabricated to strongly absorb in the near-infrared (NIR) region where light transmits deeply into tissue. When injected systemically, these particles have been shown to accumulate within the tumor due to the enhanced permeability and retention effect and induce photo thermal ablation of the tumor when irradiated with an NIR laser. Tumor specificity can be increased via functionalizing the nanoshell surface with tumor-targeting moieties. Nanoshells can also be made to strongly scatter light and therefore can be used in various imaging modalities such as dark-field microscopy and optical coherence tomography - OCT (Morton et al., 2010).

An interesting application of nanoshell research was demonstrated by Hirsch et al. (2006) by incubating human breast carcinoma cells with nanoshells *in vitro. T*he breast carcinoma cells found to have undergone photo-thermally induced morbidity on exposure to NIR light (820 nm) as determined by using a fluorescent viability stain. Cells without nanoshells displayed no loss in viability after the same periods and conditions of NIR illumination. Likewise, *in vivo* studies under magnetic resonance guidance revealed that exposure to low doses of NIR light in solid tumors treated with metal nanoshells reached average maximum temperatures capable of inducing irreversible tissue damage (ΔT = 37.4 ± 6.6°C) within 4-6 min. Controls treated without nanoshells demonstrated significantly lower average temperatures on exposure to NIR light (ΔT < 10°C). These results demonstrate a good correlation with the histological findings: tissues heated above the thermal damage threshold displayed coagulation, cell shrinkage, and loss of nuclear staining, which are all indicators of irreversible thermal damage, whereas control tissues appeared undamaged. Now that a regime of nanoshell and laser dosage has been established for successful therapy of nanoshell-treated tumors, survival studies monitoring tumor growth/regression of entire tumors after treatment with the NIR nanoshell therapy under MR guidance are possible.

Future investigation of a targeted nanoshell therapy that is similar in many ways to the delivery of stealth liposomes is warranted. In this approach, nanoshells "stealthed" with PEG are systemically injected and preferentially accumulate at the tumor site due to the highly permeable, poorly organized vascular networks commonly found in tumors

(Papahadjopoulos et al., 1991; Wu et al., 1993). This preferential accumulation behavior is often referred to as the enhanced permeability and retention effect (Maeda, 2001). NIR treatment of the bulk tissue then selectively heats and destroys the nanoshell-laden tumor regions within the tissue, leaving surrounding tissue intact. As an additional adjuvant, nanoshells may also be conjugated with antibodies targeting surface oncoproteins overexpressed by tumor cells. These antibodies would enhance target specificity and cellular internalization resulting in more selective thermal damage to the tumor. Such therapies could have a large impact on the treatment of secondary metastases and other tumors considered to be otherwise inoperable (Lal et al., 2008).

8. Conclusions

Innovative approaches are being explored in many areas of medicine to reduce costs by increasing both efficiency and effectiveness of patient care. Less invasive surgical access has allowed more rapid recovery and decreased inpatient costs for procedures ranging from laparoscopic cholecystectomy to neurosurgery for cerebral neoplasms. Advanced electronic devices including color Doppler ultrasound, open magnetic resonance imaging, and low-cost semiconductor laser fiber optics can be coupled for accurate detection and improved tumor ablation without open surgical access in many anatomic sites. Imaging guided interstitial laser therapy is minimally invasive and cab be repeated as an outpatient procedure for improved palliation of recurrent tumors. We and others have performed UTZ-guided or MRI-guided LITT during the last 18 years for unresectable and recurrent head and neck cancer.

Because head and neck cancers are accessible for surgery and have a well described loco-regional biological behavior, they are an ideal model to test combined laser energy delivered via interstitial fiber optics and chemotherapeutic agents activated by photo-thermal energy as an alternative, less invasive treatment for cancer. Long term remission and tumor eradication may be possible by combining intratumor chemotherapy with photo-thermal energy delivery via laser fiber optics. In this model, cisplatin and hyperthermia have been shown to an effective combined therapy in the laboratory and in recent clinical trials. In addition to therapeutic benefits and improved tumoricidal effects, combining intralesional anti-cancer drugs with interstitial photo-thermal laser treatment reduces systemic toxicity and is less invasive than conventional chemotherapy or surgical resection. This research will benefit from recent advances in development of low-cost imaging systems for real-time monitoring during minimally invasive procedures. Photo-chemotherapy promises to become a useful adjunctive modality for tumor palliation in advanced cancer patients and may represent one of many future biomedical applications of quantum microeletronics devices and nonothechnology in surgical oncology.

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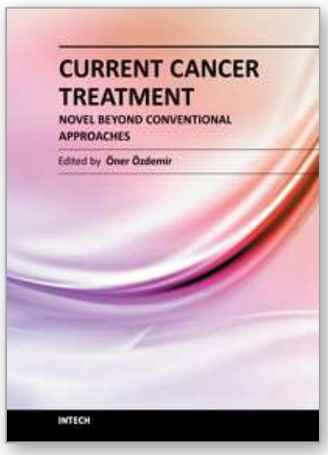
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Currently there have been many armamentaria to be used in cancer treatment. This indeed indicates that the final treatment has not yet been found. It seems this will take a long period of time to achieve. Thus, cancer treatment in general still seems to need new and more effective approaches. The book "Current Cancer Treatment - Novel Beyond Conventional Approaches", consisting of 33 chapters, will help get us physicians as well as patients enlightened with new research and developments in this area. This book is a valuable contribution to this area mentioning various modalities in cancer treatment such as some rare classic treatment approaches: treatment of metastatic liver disease of colorectal origin, radiation treatment of skull and spine chordoma, changing the face of adjuvant therapy for early breast cancer; new therapeutic approaches of old techniques: laser-driven radiation therapy, laser photo-chemotherapy, new approaches targeting androgen receptor and many more emerging techniques.

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