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New potential for enhancing concomitant chemoradiotherapy with FDA approved concentrations of cisplatin via the photoelectric effect

Yucel Altundal^{a,*}, Gizem Cifter^a, Alexandre Detappe^{b,c}, Erno Sajo^a, Panagiotis Tsiamas^b, Piotr Zygmanski^b, Ross Berbeco^b, Robert A. Cormack^b, Mike Makrigrigorgos^b, and Wilfred Ngwa^{a,b}

^aDepartment of Physics and Applied Physics, University of Massachusetts Lowell, Lowell, MA 01854, USA

^bDepartment of Radiation Oncology, Brigham and Women's Hospital, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA 02215, USA

^cUniversity of Lyon Claude Bernard, France

Abstract

We predict, for the first time, that by using United States Food and Drug Administration approved concentrations of cisplatin, major radiosensitization may be achieved via photoelectric mechanism during concomitant chemoradiotherapy (CCRT). Our analytical calculations estimate that radiotherapy (RT) dose to cancer cells may be enhanced via this mechanism by over 100% during CCRT. The results proffer new potential for significantly enhancing CCRT via an emerging clinical scenario, where the cisplatin is released *in-situ* from RT biomaterials loaded with cisplatin nanoparticles.

Keywords

Cisplatin nanoparticles; Dose enhancement; Chemoradiotherapy; Radiotherapy; Brachytherapy

Introduction

The advent of concomitant chemoradiotherapy (CCRT), characterized by synchronous administration of chemotherapy and radiotherapy (RT), has lead to major improvements in cancer treatment over the past 2 decades [1]. Currently, CCRT is the standard of treatment for many cancers in which locoregional control is necessary, while it is actively being investigated for others [1]. One of the most commonly used chemotherapy drugs for CCRT is cisplatin [1], reportedly employed to treat about 50% of all cancers [2]. In a recent work [1–4], several mechanisms of cisplatin-mediated radiosensitization have been proposed to account for the observed improvements in cancer treatment via CCRT [5,6]. Unfortunately, the radiosensitization benefits of cisplatin come with significant dose-limiting systemic

*Corresponding author. Olney Science Center, One University Avenue, Lowell, MA 01854, USA. Tel.: +1 978 934 3750, +1 978 427 0413 (mobile); fax: +1 978 934 3068. Yucel_Altundal@student.um.edu (Y. Altundal)..

toxicities including nephrotoxicity and neurotoxicity [2]. There is correspondingly clear rationale to develop new strategies for safer and more effective CCRT.

A potential strategy is to exploit the high atomic number (Z) platinum core component of cisplatin. This component could permit significant radiosensitization via photoelectric mechanism, given that the probability of photoelectric interaction with lower energy RT photons is approximately proportional to Z^3 [7]. However, until now, the photoelectric mechanism of radiosensitization by cisplatin during CCRT has been considered to be insignificant [8]. This is partly due to the relatively low concentrations of cisplatin or cisplatin nanoparticles (CNP) that reach the tumor when administered intravenously, as is customary, given the limitations posed by systemic toxicity [9,10]. This study innovatively considers a potential clinical scenario, where CNP are administered *in-situ* from RT biomaterials loaded with CNP.

Recent studies [11,12] have proposed that the inert RT biomaterials (fiducials or brachytherapy spacers), routinely implanted into tumors, for increasing spatial accuracy during RT, can be upgraded to smart biomaterials by coating the inert ones with a polymer films loaded with drugs. Once in place, the smart biomaterials can gradually or sustainably release the drugs into the tumor sub-volume as the polymer coating degrades. We hypothesize that delivering United States Food and Drug Administration (FDA) approved concentrations of cisplatin via this approach would allow achievement of sufficiently potent cisplatin concentrations in the tumor to elicit significant radiosensitization via photoelectric mechanism during CCRT. By considering FDA approved concentrations, our study importantly takes into account the crucial issue of cisplatin toxicity. Combined with the *in-situ* delivery strategy, this new approach could significantly enhance therapeutic efficacy of CCRT with cisplatin, enabling increased radiosensitization while minimizing systemic toxicity. And because the inert biomaterials are already routinely used, replacing them with the smart ones would come at no additional inconvenience to patients.

As a first step to test our hypothesis, theoretical calculations were carried out to estimate the magnitude of dose enhancement to the tumor, caused by radiation-induced photoelectrons originating from CNP released from the smart biomaterials, during external beam and internal radiotherapy (brachytherapy). The results will provide the relevant basis for further cross-disciplinary research and development that could significantly improve CCRT for lung cancer, prostate cancer, and other cancers where RT biomaterials are routinely employed.

Methods

A previously employed analytical calculation method [13,14] was employed to estimate the dose enhancement to the tumor vasculature, and hypothetical high-risk tumor sub-volume away from the tumor vasculature. The tumor vasculature was particularly considered because it represents a highly attractive target for cancer therapy, with the vasculature endothelial cells (EC) playing a crucial role in metastasis, the leading cause of mortality from cancer [13,14]. Meanwhile, studies have shown that dose enhancement or radiation boosting to high-risk tumor sub-volumes, e.g. a hypoxic/radioresistant region, could help prevent RT treatment resistance or cancer recurrence [15]. Figure 1(a) is a schematic of part

of a tumor showing the EC and high-risk tumor sub-volume, with the CNP located at the exterior. Similar to previous models [16], a uniform distribution of CNP is assumed in calculating the dose enhancement. However, here, such a uniform distribution is considered to result from the diffusion of targeted nanoparticles sustainably released *in-situ* from the RT biomaterials rather than from targeted nanoparticles delivered intravenously [17]. It is recognized that even for such a sustained *in-situ* delivery approach, a relatively uniform distribution of CNP at considered concentration distribution, maintained over the duration of RT may not be realized in practice. Tumor sub-volumes near the *in-situ* release site would likely have higher than average concentrations compared to sub-volumes further away. Therefore, calculations were done for a range of average concentrations up to the FDA approved limit. More discussion on possible consequences from these assumptions will be provided in the discussion section.

Figure 1(b) highlights the tumor EC modeled as a slab of 2 μm (thickness) $\times$ 10 μm (length) $\times$ 10 μm (width) with the CNP located on the exterior of the EC. A detailed description of this EC model and analytic calculation method has been published previously [13,14,18]. Briefly, clinically applicable Monte Carlo generated external beam radiotherapy (EBRT) photon energy spectra [19] for a 6 MV source was employed at two different depths: 1.5 cm depth ($4 \times 4 \text{ cm}^2$ field size) and 20 cm depth ($10 \times 10 \text{ cm}^2$ field size). Meanwhile, for internal RT, I-125, Pd-103, and 50 kVp spectra described in previous work [14], were used.

After photons from the above RT sources interact via photoelectric mechanism with the CNP, the kinetic energy of an emitted photoelectron is given by the difference between the photon's energy and the appropriate photoelectric absorption edge of platinum (i.e. ~ 78.4 keV for K-edge, 13 keV for L-edge, and 2.3 keV for M-edge). As described in the previous work, the number of emitted photoelectrons is obtained by multiplying the probability for photoelectric interaction by the number of incident source photons. Each of the photoelectron emitted from the CNP deposits or loses its kinetic energy locally. The energy loss for a statistical sample of photoelectrons will occur in a “sphere of photoelectron interaction” centered on the nanoparticle (Fig. 1). To estimate the energy loss, the electron energy loss equation by Cole [20] was employed. Cole determined that for electrons of 20 eV to 20 MeV, there is an empirical relation between the electron energy loss $dE/dr(\text{keV}/\mu\text{m})$ and the residual range $R(\mu\text{m})$, in unit density materials like tumor cells:

$$\frac{dE}{dR} = 3.316(R+0.007)^{-0.435} + 0.0055R^{0.33} \quad (1)$$

Here $R = R_{\text{tot}} - r$, where r is the distance from the photoelectron emission site, and R_{tot} is the total range of the photoelectron for a kinetic energy E :

$$R_{\text{tot}} = 0.431(E+0.367)^{1.77} - 0.007 \quad (2)$$

The kinetic energy deposited within the EC is calculated by integration [Eq. (3)] over the differential energy loss (dE/dr) from the surface of the CNP (R_n) to the distal side of the endothelial cell (D_E).

$$E_{\text{slab}} = \int_{R_n}^{R_n + D_E} \frac{\text{Shell}_{\text{hemisphere}} - \text{Shell}_{\text{spherical cap beyond EC}}}{\text{Shell}_{\text{entire sphere}}} \frac{dE}{dr} dr \quad (3)$$

As in the calculation model in previous studies [13,14], $\text{Shell}_{\text{hemisphere}}$ represents the surface area of a hemisphere equal to half of the sphere of interaction centered on the CNP (Fig. 1), $\text{Shell}_{\text{spherical cap beyond EC}}$ is the area of the spherical cap beyond the EC, and $\text{Shell}_{\text{entire sphere}}$ refers to the surface area of the whole sphere. The calculation essentially excludes the fraction of energy deposited in the hemispherical shell in the vasculature lumen and the spherical cap beyond the endothelial cell.

A slight modification of the integral in Eq. (3) allowed integration of the energy deposited in a high-risk tumor sub-volume modeled as a microscopic cubic slab or voxel containing a tumor cell (Fig. 1)(c). Dose enhancement or radiation boosting of such a high-risk tumor sub-volume, e.g. hypoxic (radioresistant) region with voxels obtained via Magnetic Resonance Imaging (MRI) or Positron Emission Tomography (PET) imaging, is customarily referred to as dose painting. Here, the main difference in the calculation was that the integration was computed for the cubic slab of thickness 10 μm containing the tumor cell of diameter 10 μm [21], rather than 2 μm thickness as done for the EC (Fig. 1(b)). The modified integral can be expressed as

$$E_{\text{slab}} = 2 \int_{R_n}^{R_n + D_E} \frac{\text{Shell}_{\text{hemisphere}}}{\text{Shell}_{\text{entire sphere}}} \frac{dE}{dr} dr \quad (4)$$

where E_{slab} is the kinetic energy deposited in the 10 μm cubic slab containing the tumor cell. The factor of 2 in the integral is because of the contribution from the nanoparticle on the other side of the slab. It is assumed that each neighboring microscopic tumor sub-volume or slab making up the tumor has a similar nanoparticle attached; therefore, energy that is deposited in an adjacent slab ('cross-fire') is accounted for. And, because of the assumed uniform or homogenous distribution, the specific location of the CNP outside the slab does not affect the overall calculational outcome.

Subsequent division of the energy deposited in the EC or microscopic tumor sub-volume by the mass of the EC or sub-volume, respectively, yields the additional dose from photoelectrons due to the presence of CNP. The dose enhancement factor (DEF) is then defined as

$$\text{DEF} = \frac{\text{Dose with nanoparticles}}{\text{Dose without nanoparticles}} \quad (5)$$

The DEF was calculated for a range of CNP concentrations up to the FDA approved limit of cisplatin.

To determine the concentration limit, the FDA approved dose of 100 mg/m^2 body surface area (BSA) per cycle was considered [22]. This translates to 179 mg of cisplatin for an average person with a BSA value of 1.79 m^2 [23]. A tumor volume with a default diameter 2 cm was considered; this is average size for prostate and early stage lung tumors [24,25].

This corresponds to a tumor mass of about 4.2 g, for average tumor density of 1.00 g/cm³ [26]. This would result in an average concentration of about 43 mg cisplatin per gram tumor. The calculations take into account the fact that only 65% of cisplatin is the high-Z platinum. For greater perspective, calculations were also carried out for a range of tumor volume sizes and for FDA approved cumulative dose of 300 mg/m².

Results

For CCRT with EBRT, the DEF values for representative sample field depths and field sizes are shown in Fig. 2 for a CNP concentration of 43 mg/g, which corresponds to the FDA approved one cycle dose for cisplatin for a 2 cm diameter tumor volume. Figure 2(a) shows the results for the dose enhancement to the EC (EDEF) due to photoelectrons, while Fig. 2(b) shows the dose enhancement to the high-risk tumor sub-volume (DEF). The results show that significant dose enhancement can be achieved for the different depths and field sizes. For example, for CNPs, the maximum DEF to the high-risk tumor sub-volume was calculated as 2.11 (>100%).

As would be expected, the DEF to the microscopic tumor sub-volume during EBRT is higher than that to the EC. This is because in the calculations for EC, the energy of photoelectrons deposited in the blood vessel lumen (Fig. 1) is excluded in the integration and not compensated for by cross-fire, since no nanoparticles are located in the lumen. Meanwhile, the differences in DEF for each configuration may be explained by the different external beam energy spectra obtained for different field sizes or depths. The configurations with a higher fraction of lower energy photons close to the K-edge or L-edge are mostly expected to yield a higher DEF due to increased photoelectric interactions. Similarly, the DEF mostly increases with field size given that bigger field sizes yield a higher fraction of lower energy photons due to more lateral scatter. Altogether, the results for EBRT show that significant CNP radio-sensitization via photoelectric mechanism can be achieved during EBRT.

For greater perspective, Fig. 3(a) shows the EBRT results for both single cycle and cumulative (3 cycle) FDA approved cisplatin doses, for a range of tumor volume sizes. Substantial radiation dose enhancement up to about 4.3 is obtained for cumulative cisplatin doses. As the considered tumor volume increases, the average CNP concentration reduces, and hence the average DEF decreases, as would be expected.

For CCRT with internal RT our calculations (Fig. 3(b)) predict that higher DEF values than for EBRT can be achieved with values greater than 4.00 and up to ca. 14.00 for cumulative CNP doses. The higher DEF values for internal RT are consistent with expectations of higher photoelectric interactions at lower kV photon energies typically employed for internal RT.

Interestingly, the DEF values to the high-risk tumor sub-volume when using 50 kVp or I-125 sources is higher than for Pd-103 despite the fact that Pd-103 has a lower average photon emission energy, closer to the L-edge of platinum (about 13 keV), which would typically translate to a higher probability of photoelectric interactions and hence higher

photoelectron production. This may be explained by the fact that despite the higher production rate, the Pd-103 induced photoelectrons have lower kinetic energy to deposit within the tumor sub-volume when compared to the other sources. On the other hand, for endothelial cells, Pd-103 has a higher DEF. This may be due to the smaller thickness of the endothelial cell (2 μm), with most of the energy from emitted Pd-103 photoelectrons, which have shorter range [Eq. (2)] deposited in the EC. For the other sources (50 kVp and I-125) with relatively higher energies and hence range, a major portion of the kinetic energy is deposited outside of the EC, in the vasculature lumen, and is not compensated for by cross-fire unlike the case with tumor sub-volume.

Discussion

Our theoretical results indicate that FDA approved concentrations of cisplatin could yield significant dose enhancement to the highly sensitive tumor vasculature endothelial cells, as well as major radiation boosting to the tumor sub-volume via photoelectric mechanism during CCRT with either EBRT or internal RT. Application-wise, a dose enhancement factor (DEF) of 2.00 (i.e., 100%) means doubled radiation dose to the target. Clinical studies indicate that such radiation boosting helps to prevent cancer recurrence and leads to significant increase in survival for cancer patients [27,28]. One study reports that every 1 J/kg boost in biologically effective dose (BED) is associated with 4% relative improvement in survival for lung cancer patients [28]. Therefore, the impact of doubling the RT dose would be significant. However, current modalities for radiation boosting are critically limited by normal tissue toxicity [27]. An American medical task group report notes that new treatment strategies that can overcome these limitations, allowing an increased dose to the tumor while sparing normal tissue, will significantly improve the balance between complications and cure [27]. Based on the results of this study, there is potential to do this, since the dose enhancement from the micrometer-range electrons resulting from the photoelectric effect is more highly localized. This would enable substantial radiation boosting to tumors or important targets within the tumor without significant increase in normal tissue toxicity during CCRT.

In the *in-situ* delivery approach assumed in this study, routinely used inert RT biomaterials would be replaced by smart RT biomaterials with polymer coating loaded with the high-Z CNP. Once in place, the smart RT biomaterials can then release the CNP as the polymer coating degrades. A number of recent studies have reported the design of CNP that would enhance cisplatin delivery in the tumor [2,29,30]. The feasibility of incorporating such nanoparticles in novel smart biomaterials has also been demonstrated recently where inert biomaterials were coated with biodegradable, biocompatible chitosan films containing nanoparticles loaded with a drug model for sustainable release as the polymer degrades [12]. A similar approach could be used to develop the smart RT biomaterial loaded with CNP. Alternatively, CNP can be incorporated in poly(D,L-lactide-co-glycolide) (PLGA) polymer millirods during the gel phase of production [31,32]. The results here provide impetus for more research to develop such next generation RT biomaterials.

In the current study, it is assumed that the administered concentration of CNP at the FDA approved concentrations would uniformly distribute and reside in the tumor region of

interest during RT. However, even for CNP actively targeted to bind to tumor cells as shown in recent studies [2], some of the CNP may escape e.g. via the tumor-draining vasculature. Hence the maximum DEF values obtained here may not be reached in practice, purely from such a consideration. Notwithstanding, as the DEF estimates for a range of concentrations and tumor volume sizes show, substantial sub-volume radiation boosting could be achieved even for cisplatin levels less than the FDA approved cumulative dose. Further work will determine ways to optimize the distribution and sustained level of CNP concentrations that reside within the tumor sub-volume during RT to maximize sub-volume RT boosting.

A number of possibilities exist to customize the intra-tumor biodistribution of the CNP released *in-situ* from the smart RT biomaterials in order to optimize the intra-tumor biodistribution and enhance CCRT therapeutic ratio. For example, the CNP release may be customized by modifying the smart RT biomaterial's degradation time (polymer coating properties or cross-linking) as optimal for CCRT treatment schedule. The radiation boost could also be customized by varying the 3-dimensional intra-tumor biodistribution over time as function of CNP size, shape, initial concentration etc. Furthermore, the CNP could be functionalized, as mentioned above, with moieties actively targeting molecular epitopes on tumor cells [2,33]. The location of the smart biomaterial could also be optimized by ensuring the biomaterial is near the target high-risk tumor sub-volume where radiation boosting is most needed. In this way, even if the intra-tumor biodistribution is not homogenous, the high-risk tumor sub-volume may still receive major radiation boosting since a high concentration of the CNP would likely reside in this region of interest. Studies show that selective boosting of such high-risk tumor sub-volumes, e.g., sub-volumes with hypoxic or radio resistant cells or sub-volumes with cancer stem cells could lead to more effective treatment outcomes [34]. Such high-risk tumor sub-volumes can be identified in the clinic via functional imaging methods like MRI or PET. In any or a combination of these different ways, the RT boosting can potentially be tailored to different tumors or patients and treatment schedules during CCRT. The results in this study motivate further studies to investigate these different possibilities for customization.

Recent studies indicate that the distribution of high-Z nano-particles (NPs), e.g. gold NPs, within the tumor and inside the cells may not be homogenous [35–37]. In a Monte Carlo study, Cai et al. showed that dose enhancement is highly sensitive to subcellular location of NPs [38]; for the same initial photon energy and the number of NPs per cell, DEF values increase as the location of NPs get closer to the nucleus of the cell. In the calculations in the current work, it was assumed that the CNP are located on the exterior of the cell or tumor sub-volume. This is a conservative location for the CNP with respect to the calculation results. In practice, cisplatin's effectiveness lies in how easily it releases its platinum molecule, freeing it to cross-link DNA strands, disrupting cell division and forcing the cell to undergo apoptosis [1]. Because of this mechanism, it is more likely that a significant number of photon-induced electrons will be emitted from within the nucleus or cytoplasm after endocytosis of CNP by tumor cells. Such a scenario should lead to higher DEF values than estimated and more damage to tumor DNA consistent with the findings of Cai et al. When dose enhancement contribution from short range Auger electrons [39–41] is taken into account, it is expected that the DEF values calculated here may become higher.

Cai et al. also showed that DEF values are linearly dependent on number of NPs per cell, which agrees with the findings of our work. They further investigated the DEF values for different cell models, e.g., monolayer (2D) and a cluster of cells (3D), which are conceptually similar to the EDEF and DEF calculations in our work. As expected, they also found that dose enhancement values are higher for a cluster of cells compared to the monolayer distribution of cells, for the same initial photon energy and NP concentration.

In the calculations, it was also assumed that the CNP are located on the exterior of the cell or tumor sub-volume. This is a conservative location for the CNP with respect to the calculation results. In practice, cisplatin's effectiveness lies in how easily it releases its platinum molecule, freeing it to cross-link DNA strands, disrupting cell division and forcing the cell to undergo apoptosis [1]. Because of this mechanism, it is more likely that a significant number of photon-induced electrons will be emitted from within the nucleus or cytoplasm after endocytosis of CNP by tumor cells. Such a scenario could lead to higher DEF values than estimated and more damage to tumor DNA. Also, results for other FDA approved platinum-based chemotherapy drugs like carboplatin, and oxaliplatin will be investigated.

One advantage of *in-situ* delivery compared to typical systemic administration is that the tolerance to systemic toxicity would be much higher, which could provide room to further minimize potential toxicities or employ higher *in-situ* concentrations if needed. One study in mice showed that *in-situ* delivery increased the maximum tolerated dose of cisplatin by 5 times compared to systemic delivery [42]. When considered together with the ability for RT boosting without increase in normal tissue toxicity, the potential broader impact of the new approach motivated by the current study results could be very significant for lung and prostate cancer patients, among others, who routinely use RT biomaterials.

Conclusion

The current limitations of CCRT with cisplatin include dose-limiting systemic toxicities and intrinsic or acquired resistance. The results in this study proffer a potential new strategy to overcome these limitations via sub-volume radiation boosting using FDA approved concentrations of cisplatin delivered *in-situ* at virtually no additional inconvenience to patients. The results provide impetus for further interdisciplinary research towards development and optimization of this potential new therapeutic strategy for safer and more effective CCRT.

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Figure 1.

(a) Schematic showing tumor section with vasculature and CNP. (b) Endothelial cell model for calculating DEF for tumor endothelial cells. (c) Model for calculating DEF to high-risk tumor sub-volume (Figures not to scale).

Figure 2.

Dose enhancement factor as a function of local nanoparticle concentration. The top line is for 20 cm depth, the bottom line is for 1.5 cm depth. (a) Tumor vasculature endothelial cells with 43 mg/g of CNP (b) high-risk tumor sub-volume with 43 mg/g of CNP.

Figure 3.

(a) DEF as a function of tumor size for single and cumulative doses of cisplatin during CCRT with EBRT (20 cm depth 10 cm $\times$ 10 cm); (b) DEF for different concentrations when brachytherapy photon sources are considered instead of EBRT.