Chapter

NQO1-Bioactivatable Therapeutics as Radiosensitizers for Cancer Treatment

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Abstract

Developing cancer therapeutics that radiosensitize in a tumor-selective manner remains an ideal. We developed a novel means of radiosensitization, exploiting NAD(P)H:Quinone Oxidoreductase 1 (NQO1) overexpression, and lowered catalase expression in solid human tumors using NQO1-bioactivatable drugs. Non-small cell lung (NSCLC), pancreatic (PDAC), prostate, and breast cancers overexpress NQO1. Ionizing radiation (IR) creates a spectrum of DNA lesions, including lethal DNA double-strand breaks (DSBs), and mutagenic but rarely lethal altered DNA bases and DNA single-strand breaks (SSBs). NQO1-bioactivatable drugs (e.g., β-lapachone and deoxynyboquiones) also promote abasic DNA lesions and SSBs. These hyperactivate poly (ADP-ribose) polymerase 1 (PARP1) and dramatically increase calcium release from the endoplasm reticulum (ER). Exposure of human cancer cells overexpressing NQO1 to NQO1-bioactivatable drugs immediately following IR, therefore, hyperactivates PARP1 synergistically, which in turn depletes NAD+ and ATP, inhibiting DSB repair. Ultimately, this leads to cell death. Combining IR with NQO1-bioactivatable drugs allows for a reduction in drug dose. Similarly, a lower IR dose can be used in combination with the drug, reducing the effects of IR on normal tissue. The combination treatment is effective in preclinical animal models with NSCLC, prostate, and head and neck xenografts, indicating that clinical trials are warranted.

Keywords: NQO1 expression, PARP hyperactivation, abasic site synergy, NAD+/ATP losses, DSB repair inhibition, programmed necrosis

1. Introduction

For decades, radiobiologists and physician-scientists have collaborated to develop effective combination therapies with ionizing radiation and radiosensitizing agents to reduce the overall dose of radiation required in cancer therapy. This minimizes adverse side-effects observed in normal tissues and increases the efficacy of radiation in reducing tumor burden. Here, we discuss the pros and cons of radiosensitizing
agents used in the clinic in comparison with NAD(P)H quinone oxidoreductase-1 (NQO1)-bioactivatable drugs. β-Lapachone (β-Lap) is a clinical chemotherapeutic agent discovered to be a potent DNA repair inhibitor in the late 1980s. It has since been shown to be bioactivated by NQO1, an enzyme elevated more than 20-fold in most solid human cancers, e.g., non-small cell lung, pancreas, prostate, head and neck, and breast cancers, and shows promise as a potent radiosensitizer.

2. Radiotherapy as a single agent

2.1 Initial use of ionizing radiation

The late 19th-century discovery of the X-ray by Wilhelm Roentgen led to diagnostic tools and therapies for diseases such as blood disorders and benign and malignant growths [1, 2]. Initially, radiation was delivered using unfocused beams, causing skin and blood malignancies in both patients and radiologists [1, 2]. Today, patients benefit from vast technological improvements, allowing for focused radiation beams, which markedly increased patient survival. Current approaches include conformal radiation therapy, proton beam radiation therapy, stereotactic radiation therapy (using linear accelerators or gamma knife devices), and intraoperative therapy [3]. Despite improvements in targeting tumors and reducing normal tissue damage, high doses of radiation are still required for a curative effect. Some tumors can also be resistant to radiotherapy, including hypoxic tumors and dormant cancer cells that regrow when the optimal tumor microenvironment presents itself. Thus, methods to improve the safety and efficacy of ionizing radiation were initiated, including combination with chemotherapeutics or radiosensitizers.

2.2 Enhancing radiation therapy with radiosensitizers

Radiosensitizing agents are molecules that enhance the dose of ionizing radiation delivered to a patient’s tumor. The optimal clinical radiosensitizer (a) lowers the required dose of ionizing radiation, (b) increases its antitumor effect, and (c)

| Radiosensitizer       | Tumor type   | Mechanism              |
|-----------------------|--------------|------------------------|
| Hyperbaric oxygen     | Brain tumors | Oxygenation             |
| Nicotinamide          | Glioblastoma | Oxygenation             |
| Metronidazole         | Cervical cancer | Oxygenation         |
| Mitomycin-C           | Breast cancer | Kills hypoxic cells |
| 5-fluorouracil (5FU)  | Gastrointestinal | S-phase check points |
| Bromodeoxyuridine (BrDU) | Breast       | Repair inhibition |
| Topo-inhibitors       | Breast, cervical | DNA damage       |
| NBTXR3                | Solid tumors | Direct                  |
| Nimoral               | Head and neck | Modifies hypoxia       |
| Trans sodium crocetinate | Glioblastoma | Oxygenation             |
| NVX108                | Glioblastoma | Oxygenation             |

List of commonly used radiosensitizing methods/agents for combination with radiotherapy in various tumor types. The last four are emboldened to denote their current use in ongoing clinical trials.

Table 1. Clinical radiosensitizers.
synergistically kills cancer cells. To date, no radiosensitizer has met these demands. Many radiosensitizers have been used clinically (Table 1, normal text) with limited success, or are currently in clinical trial (Table 1, bold text). These include suppressors of radioprotectors (e.g., thiol) [4], molecules releasing cytotoxic substances when radiolyzed [5], thymine/cytidine analogs [6], oxygen mimic sensitizers [7], and DNA repair inhibitors [8].

3. β-Lapachone, a DNA repair inhibitor

3.1 Initial discovery of β-lapachone’s effect on DNA repair

In the late 1980s, our laboratory began searching for DNA repair modulators that synergize with ionizing radiation to kill cancer cells more effectively. The goal was to thwart cancer cells’ ability to repair IR damage, to avoid the survival of IR-resistant malignant cells that have undergone potentially lethal damage repair (PLDR). One of those compounds was (3,4-dihydro-2,2-dimethyl-2H-naphthol[1,2-b]pyran-5,6-dione), also known as β-lapachone [9].

We found that just four micromolar β-lapachone inhibited single-strand DNA break repair in cancer cells exposed to DNA-damaging agent methyl methane sulfonate [9, 10], killing 99% of cells at an exposure time 90–120 min [11]. Additionally, we found that combining β-lapachone with ionizing radiation in Hep2 cells increased double-strand breaks and dramatically lowered the dose of radiation required for cell death, highlighting β-lapachone as a potent radiosensitizer [12].

In the 1990s and early 2000s, we conducted subtraction-hybridization screening to isolate X-ray inducible genes to investigate ionizing radiation resistance and found Xip3, also known as NQO1 [13]. Dicoumarol, an NQO1 inhibitor, specifically blocked β-lapachone’s toxicity, indicating that the radiosensitizer may be bioactivated by this enzyme. As NQO1 is specifically expressed in tumor cells, this indicated a promising use of β-lapachone as a cancer therapeutic with or without ionizing radiation.

4. Mechanism of action for NQO1-bioactivatable therapies

4.1 NQO1 vs. catalase ratio and specificity

NQO1 is a Phase II detoxification enzyme that reduces ROS levels in cancer cells. NQO1 converts quinones into stable intermediate hydroquinones that are exported out of the cell by conjugation [10]. Most solid cancers, including non-small cell lung and pancreatic cancers (>85%), prostate, colon, and breast cancers (60%) and head and neck cancers (40%) overexpress NQO1 5- to 200- fold above normal tissue. Corresponding levels of catalase in these cancers were strikingly reduced, impacting the ability of cancer cells to eliminate ROS [14]. Overexpression of NQO1 appears to stabilize HIF-1alpha and promotes metastasis [15].

Though NQO1 detoxifies most quinones through two-electron oxidoreduction, a few quinones undergo a rapid futile redox cycle response, generating an unstable intermediate hydroquinone that spontaneously reverts back to its original form using two oxygenation steps and creating two superoxides. Deoxynypyruvones (DNQ), KP372 agents, and β-lapachone are three classes of NQO1-bioactivatable drugs currently known [16]. Recently, Napabucasin, an orphan drug in clinical trials for pancreatic and cervical cancer, has also been reported to be bioactivated by NQO1 [17]. Though mitomycin C and streptonigrin are metabolized by NQO1,
these agents can also be activated by other drug metabolizing enzymes [18]. Human cancer cells overexpressing NQO1 have been shown to be sensitive to NQO1-bioactivatable drugs alone and in combination with PARP inhibitors, cisplatin, radiation, and NAMPT inhibitors both in cell culture and xenograft models [14, 19].

4.2 NQO1-dependent ROS formation and PARP hyperactivation

Cancer cells overexpressing NQO1 and exposed to NQO1-bioactivatable drugs, such as β-lapachone, DNQ or IB-DNQ, acquire extensive DNA lesions as evidenced by alkaline comet assays [11]. The unstable hydroquinone form of these NQO1 bioactivatable drugs reacts with two oxygen molecules spontaneously to regenerate the original compound [20]. This futile redox cycle consumes ~60 moles of NADPH to generate ~120 moles of ROS in ~2 min for β-lapachone, leading to the generation of permeable hydrogen peroxide (H₂O₂). This diffuses into the nucleus and causes massive oxidative stress and SSBs [16]. Initial DNA damage is mainly through the formation of altered bases, SSBs, and apurinic/apyrimidinic (AP) sites generated through incorporation of 8-oxo-deoxyguanine [21]. Ultimately, damage caused by H₂O₂ results in extensive SSBs and DSBs. These lesions lead to PARP hyperactivation that can be prevented by BAPTA-AM (chelates Ca²⁺), PARP inhibitors, or the NQO1 inhibitor dicoumarol, in NQO1+ cells. In contrast, cells deficient in NQO1 due to NQO1 polymorphisms, *2[C609T] or *3[C465T], are unaffected by exposure to NQO1-bioactivatable compounds [14], lacking the enzyme activity for redox cycling. Hyperactivation of PARP rapidly degrades the increased NAD+ pools generated as a result of the oxidation of NADH in the futile cycle [11, 20, 22]. NAD+ loss is not seen in cells treated with PARP1 inhibitors; instead, cells exposed to PARP inhibitors in combination with NQO1-bioactivatable drugs undergo a synergistic apoptotic cell death response [14].

4.3 Calcium release, DNA damage and μ-Calpain-dependent programmed necrosis

One of the key components in the cell death response by NQO1-bioactivatable drugs is the release of calcium from the core endoplasmic reticulum (ER) stores, which is otherwise inert [11, 23]. This results in specific programmed necrosis referred to as NAD⁺-KERESIS. Pre-treatment, with the calcium chelator, BAPTA-AM, suppresses PARP hyperactivation and results in specific inhibition of NQO1-dependent cell death by NQO1-bioactivatable drugs. Extensive DNA damage along with Ca²⁺ release from the ER results in the hyperactivation of PARP1 in NQO1+ cancer cells. PARP1 hyperactivation rapidly degrades the NAD+ and causes concomitant ATP losses within 30–40 min of drug treatment. μ-Calpain activation is observed upon treatment with NQO1-bioactivatable drugs within 8–24 h [16, 24]. The multitude of damage caused by treatment with these drugs overwhelms DNA repair machinery and depletes the cells of the energy resources, culminating in cell death [10, 11, 16, 20, 24–27].

4.4 NQO1-bioactivatable drugs lead to perturbations in metabolic pathways

Treatment with NQO1-bioactivatable drugs causes wide-scale metabolic changes in the cell, which can be attributed to cell death overwhelming the cellular machinery. Altering key enzymes in NAD metabolism results in synergy with NQO1-bioactivatable drugs. NAMPT is an important source of reducing equivalents for redox balance in cancer cells. Pretreatment with FK866, a NAMPT inhibitor, leads to accelerated cell death due to decrease in NAD+/NADH levels and reduced doses
of NQO1-bioactivatable drugs [28]. NAMPT knockdown has also been shown to sensitize cancer cells to ROS induction through ionizing radiation [29, 30].

4.5 Exploiting NQO1-bioactivatable drugs as radiosensitizers

Cancer cells, tissues, and organs subjected to ionizing radiation experience a wide spectrum of DNA lesions including SSBs, DSBs, AP sites and DNA-protein cross-links. One unrepaired DSB is lethal to the cell [21, 31]. Hence, NQO1-bioactivatable drugs, when combined with IR (Figure 1), synergistically kill cancer cells due to the combined effect of DNA damage and PARP1 hyperactivation [21, 32]. Sublethal doses of NQO1 drugs and IR combine to release massive amounts of ROS due to

Figure 1.
Radiation sensitization by NQO1 bioactivatable drugs: sublethal doses of β-lapachone when bioactivated by NQO1 release massive amounts of ROS, resulting in synergy with IR and increased programmed necrosis. NQO1 bioactivatable drugs in combination with IR show tremendous synergy even at low doses. The combined effect of DNA damage and PARP hyperactivation provides more lethality to a cancer cell whereas NQO1 provides the specificity. This leads to increased ROS, γH2AX formation, hyperactivation of PARP, massive NAD and ATP losses, prevention of DSB repair, perturbations in the metabolic pathways, and μ-Calpain-mediated programmed necrosis known as NAD+ -Keresis.

Figure 2.
Sublethal doses of IR and β-lap in NQO1+ LNCaP cells cause PARP-1 hyper-activation and dramatic ATP loss: A, LNCaP cells expressing or lacking NQO1 were treated with IR + β-lap and monitored for PAR formation—UT, untreated control for IR; V, vehicle; DMSO only. B, Synergistic ATP loss was noted after IR + β-lap compared to single treatments alone. Results are means ± SE for experiments performed three times in duplicate. Student’s t-tests compared single to combined treatments. **p < 0.01, ***p < 0.001.
their synergy, resulting in PARP hyperactivation, loss of nucleotides and increased programmed necrosis (Figures 2 and 3), beyond the capabilities of the single agents (IR or NQO1-bioactivatable drug) alone. Head and neck cancers, PDA and NSCLC...
have been shown to be sensitive to nontoxic doses of \( \beta \)-lapachone when combined with IR \([21, 32]\). Using NQO1-bioactivatable drugs as radiosensitizers leads to increases in ROS, \( \gamma \)H2AX formation, hyperactivation of PARP1, massive NAD\(^+\) and ATP losses, inhibition of DSB repair, perturbation in carbon flux pathways and \( \mu \)-Calpain mediated programmed necrosis known as NAD\(^+\)-Keresis. The cell death responses observed are independent of any oncogenic drivers \([21, 31–33]\). This lethal combination between radiation therapy and NQO1-bioactivatable drugs prolongs long-term survival and promotes enhanced tumor shrinkage at non-toxic doses of each agent (IR and Drug, Figure 4). Thus, combining NQO1-bioactivatable drugs with radiation therapy, should be a long-standing treatment modality for tumors overexpressing NQO1.

5. Discussion

5.1 Advantages of NQO1-bioactivatable drugs vs. other radiosensitizers

The major advantage of using NQO1-bioactivatable drugs as radiosensitizers is the tumor selectivity afforded by the drugs themselves. Synergy is afforded by a number of tumor-selective responses to the drugs. First, the dependence of the drugs on NQO1 levels is perfect for the specific treatment of various difficult-to-treat human cancers, including non-small cell lung, pancreatic, breast, prostate, and head and neck cancers. Tumor selectivity requires approximately 100 units of enzyme activity, whereas lower levels of NQO1 results in mild metabolomic alterations used for the treatment of metabolic syndromes \([34]\). Second, the minimum time of exposure of 30–120 min fits the pharmacokinetics of the drug. It should be noted that all studies thus far indicate that the drugs have to be available immediately after or at the same time as exposure with IR. Pre-treatment prior to IR is ineffective. Third, synergy between NQO1-bioactivatable drugs and IR occurs due to PARP1 hyperactivation causing massive NAD\(^+\) and ATP loss, preventing repair of the DNA damage created by IR. NQO1-bioactivatable drugs are highly specific to tumors, causing little normal tissue toxicity, which is unaffected by IR treatment \([14, 16, 20, 25, 31]\). Preclinical in vivo data suggest that radiosensitization trials with NQO1-bioactivatable drugs are warranted for non-small cell lung, pancreatic, breast prostate, and head and neck cancers.

5.2 Future directions for NQO1-bioactivatable drugs

A clinical trial of radiation sensitization effects of the new drug, isobutyldeoxyxyboquione (IB-DNQ), against non-small cell lung (NSCLC) and/or pancreatic adenocarcinomas (PDAC) is warranted. These cancers are almost uniformly NOQ1 over-expressive and they have routinely low levels of catalase \([14]\). We have developed CLIA assessments of NQO1 status and enzymatic levels for these studies. The pharmacokinetics of IB-DNQ in these cancers, particularly in NSCLC and PDAC cancers, is relatively short at about 6 h, but long enough for sensitization of tumors to the NQO1-bioactivatable drug + IR. Biomarker and DSB repair kinetics are ongoing in our laboratory in preparation for these radiosensitization studies.

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