A Light in Multidrug Resistance: Photodynamic Treatment of Multidrug-Resistant Tumors

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Key Words
Multidrug resistance • Visible light • Phototherapy • Photosensitizer • Review

Abstract
The major drawback of cancer chemotherapy is the development of multidrug-resistant (MDR) tumor cells, which are cross-resistant to a broad range of structurally and functionally unrelated agents, making it difficult to treat these tumors. In the last decade, a number of authors have studied the effects of photodynamic therapy (PDT), a combination of visible light with photosensitizing agents, on MDR cells. The results, although still inconclusive, have raised the possibility of treating MDR tumors by PDT. This review examines the growing literature concerning the responses of MDR cells to PDT, while stressing the need for the development of new photosensitizers that possess the necessary characteristics for the photodynamic treatment of this class of tumor.

Received: March 21, 2003
Accepted: March 24, 2003
DOI: 10.1159/000071155

Multidrug Resistance

The term multidrug resistance (MDR) is used for certain tumor cells with the ability to evade the cytotoxic effects of a broad range of structurally and functionally unrelated drugs [6, 10]. Two molecules are mainly related to this phenotype, the P-glycoprotein (Pgp) and the multidrug resistance-associated protein 1, although this phenomenon involves a multitude of factors. Both proteins belong to the ATP-binding cassette family of transporters and are thought to help pump drugs out of the cytoplasm [10, 16, 32]. These proteins were initially isolated from tumor cells with the MDR phenotype, but are also expressed in a number of normal cells in mammalian organs, including the kidney, intestine, testis, adrenal gland and lung [22, 53].

The treatment of MDR tumors refractory to conventional chemotherapy is presently the major concern of oncologists, because these tumors need additional drugs to overcome the phenotype. The use of MDR modulators, such as verapamil [57], cyclosporin A [50] and phenothiazines [7, 42], has been suggested to circumvent this problem, but the most important limitation of this association is the high toxicity of treatment.

To avoid toxicity resulting from the use of high doses of chemotherapeutics, analogues of these substances, as
well as new compounds, have been produced and selected for their potential in modulating the MDR phenotype. A number of second- and third-generation Pgp modulators are being evaluated, but despite these efforts, the mechanisms of action of those modulators are poorly understood. Moreover, the elimination of Pgp-overexpressing cells through the combined use of chemotherapeutics and Pgp modulators may lead to the selection of cells presenting alternative MDR mechanisms. Therefore, cancer therapy is in urgent need of a purging technique directed against drug-resistant tumor cells.

Photodynamic Action: A Brief History

In 1900, it was observed that the inactivation of paramecia by certain dyes occurred with illumination of the cultures [41]. This was the first published report of a photodynamic effect. Soon after, it was demonstrated that the inactivation of cells by a dye in the presence of light is dependent on molecular oxygen [25].

The term photodynamic action (PDA) was first defined in 1941 as the photo-oxidation of biological substrates in the presence of molecular oxygen and a sensitizing agent, named a photosensitizer [1]. Since then, a number of studies have been performed using different dyes, illumination conditions and biological targets, contributing to the understanding of the mechanisms of PDA. The first observations that PDA could be used for the detection and management of some types of tumors were made in 1967 [11, 28], and in 1973, the potential use of the PDA of hematoporphyrin derivatives in the treatment of tumors was established [4], initiating a series of studies of what is presently called photodynamic therapy (PDT). However, at that time, many scientists were skeptical about how light could penetrate human tissues deeply enough to have an effect on cancer. Moreover, as the first laser was built only in 1960, early medical lasers were oversized and costly tools.

Almost 20 years of research and thousands of clinical trials were necessary before PDT was finally accepted as a new cancer treatment. In the last decade of the 20th century, the good results of a number of animal experiments and clinical trials resulted in the approval of a hematoporphyrin derivative, known as porfimer sodium and commercially named Photofrin® (QLT Phototherapeutics, Vancouver, B.C., Canada), for the prophylactic treatment of papillary bladder cancer in patients with a high risk of recurrence. This authorization occurred first in Canada, followed by the Netherlands, France and Germany. In Japan, the use of PDT was approved for the treatment of patients with early and advanced stages of cancer of the lung, as well as of the digestive and genitourinary tracts [5]. In the US, Photosfrin was approved by the FDA for clinical use in patients with completely obstructing esophageal cancer and for the treatment of microinvasive endobronchial non-small cell lung cancer for which radiotherapy or surgery was not indicated [48].

Mechanisms of PDA

A photosensitizer is a molecule that is activated to an excited singlet state when it absorbs a photon of an appropriate wavelength; it can then react with biological targets, undergoing mainly three types of reactions [24, 51], as depicted in figure 1. Once in the excited singlet state, the dye can react directly with biomolecules, leading to the formation of photoadducts (type III reactions). However, the excited molecule may decay to a triplet excited state, and the subsequent reactions are essentially classified as PDA; the triplet excited dye can follow redox reactions with biomolecules, leading to the production of reactive oxygen species (type I reactions), or it can react with molecular oxygen, leading to the formation of singlet oxygen (${{{1}}}_O_2$), which is a highly reactive oxygen species. ${{{1}}}_O_2$ is generally accepted as the main damaging species in PDA, although other reactive oxygen species may also be involved in the process [60].

Therefore, the cellular effects of PDA depend on at least 4 factors: the concentration of the dye, the concentration of $O_2$, and the appropriate wavelength and intensity of the light.

Advantages and Limitations of PDT

PDT has several advantages. First, it works on virtually all types of cancers, lacking the specificity of chemotherapeutics and radiation. The procedure can be repeated several times, if needed, because there are no cumulative toxic effects, and it is usually an outpatient procedure. Moreover, because of its lower risk profile, it can be used even in the elderly or in people who are too sick for surgery. The main side effect is sensitization to light, and because of this, patients undergoing PDT need to avoid direct sunlight and bright indoor light for at least 6 weeks.

Notwithstanding the benefits described above, there are some important limitations to PDT. The photosensi-