Journal of Photochemistry and Photobiology B: Biology 150 (2015) 60–65

Contents lists available at ScienceDirect

Journal of Photochemistry and Photobiology B: Biology

journal homepage: www.elsevier.com/locate/jphotobiol

The potential application of photodynamic therapy in drug-resistant tuberculosis

Ji-Eun Chang [a], Chul-Ho Oak [b], Nackmoon Sung [c], Sanghoon Jheon [a,d,*]

[a] Department of Thoracic and Cardiovascular Surgery, Seoul National University Bundang Hospital, Seongnam-Si, Gyeonggi-do, Republic of Korea
[b] Department of Internal Medicine, Kosin University College of Medicine, Seo-gu, Busan, Republic of Korea
[c] Clinical Research Center, National Masan Tuberculosis Hospital, Gyeongnam, Republic of Korea
[d] Department of Thoracic and Cardiovascular Surgery, Seoul National University College of Medicine, Seoul, Republic of Korea

ARTICLE INFO

Article history:
Received 31 October 2014
Received in revised form 30 March 2015
Accepted 5 April 2015
Available online 16 April 2015

ABSTRACT

Tuberculosis (TB) is an infectious bacterial disease that has historically created a high global health burden. Unfortunately, the emergence of drug-resistant TB (DR-TB), which includes multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB), has greatly affected the treatment of TB. Anti-TB chemotherapy drugs are classified into five groups to facilitate application of effective guidelines for the treatment regimen. However, chemotherapy has a limited ability to treat DR-TB, and therefore a novel alternative treatment for DR-TB is required. In this review, we focused on photodynamic therapy (PDT) as potential treatment for DR-TB. PDT is a widely used cancer treatment that combines photosensitizers and harmless laser light to produce reactive oxygen species that selectively damage the target cells. Initially, PDT was originally developed to target pathogenic microorganisms but fell into disuse because of adverse reactions. Recently, photodynamic antimicrobial chemotherapy is attracting attention again as an alternative treatment for bacterial infections. In our previous study, we suggested that PDT could be a novel option to treat MDR- and XDR-TB *in vitro*. Despite the limited previous studies regarding PDT in TB models, fast-developing bronchoscopic technologies and clinician experience will soon facilitate the clinical application of safe and minimally invasive PDT for TB.

1. Introduction

Tuberculosis (TB) has become a leading cause of death from bacterial infectious disease worldwide over the past few decades. It is caused by the *Mycobacterium tuberculosis* which is a highly contagious, airborne, slow-growing, Gram-positive bacillus [1]. Humans are the primary host for *M. tuberculosis*. Unfortunately, the evolution of drug-resistant TB (DR-TB) has rapidly increased the related mortality rate and virulence of infection. In 2012, 1.3 million people died due to TB, and an estimated 170,000 of these deaths were caused by DR-TB [2]. Therefore, the World Health Organization (WHO) proposed a 'Stop TB Strategy' to reduce the global burden of disease caused by TB [2].

Photodynamic therapy (PDT) is a promising treatment for various cancers [3]. When the PDT photosensitizers are administered systemically, they are selectively taken up by the tumor tissues, and the low power laser light of a certain wavelength produces highly reactive, cytotoxic singlet oxygen, which subsequently leads to tumor cell death [4,5]. At first, PDT was used to treat pathogenic microorganisms more than a hundred years ago [6]. However, the potential of its photoantimicrobial nature was forgotten for several decades for various reasons such as many adverse reactions, the poor response of Gram-negative bacteria, and the discovery of novel antibiotics [6,7].

In recent years, given the emergence of antibiotic-resistant bacteria, PDT has re-emerged as an alternative treatment for bacterial diseases. Many researchers have studied methicillin-resistant *Staphylococcus aureus* (MRSA) [8–10] and pathogenic Vibrio [11] using photoantimicrobial agents. Previous studies have also reported that PDT is effective in treating various infections, such as *Mycobacterium fortuitum* [12], *Mycobacterium bovis* BCG [13], and *Mycobacterium marinum* [14]. In 2013, we reported that PDT effectively inactivated *M. tuberculosis*, including multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB), which suggests that PDT could potentially be an effective alternative therapy for DR-TB [7].

* Corresponding author at: 82Gumi-ro, 173beon-gil, Bundang-gu, Seongnam-si, Gyeonggi-do 463-707, Republic of Korea. Tel.: +82 31 787 7133; fax: +82 31 787 4050.
E-mail address: jheon@snu.ac.kr (S. Jheon).

http://dx.doi.org/10.1016/j.jphotobiol.2015.04.001
1011-1344/

In this review, we focused on PDT as a potential clinical application in MDR- and XDR-TB. Previous studies of *in vitro* and *in vivo* photodynamic antimicrobial chemotherapy and the recent development of clinical technologies are also discussed.

2. The emergence of drug-resistant tuberculosis

Until the middle of the 20th century, TB was thought to be an incurable disease but development of anti-TB drugs changed this [15]. However, the subsequent emergence of DR-TB soon became a major global public health concern [16,17]. The genetic resistance of TB arises from the spontaneous chromosomal mutation of *M. tuberculosis* at a low frequency [15,18]. In addition, acquired resistance to anti-TB drug treatment can occur due to irregular drug supply, inappropriate drug prescription, and patient nonadherence [18–20]. A diagram for the development of DR-TB is shown in Fig. 1 [18].

DR-TBs are commonly classified as multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) [17]. MDR-TB is caused by *M. tuberculosis*, and is defined as TB that is resistant to at least two of the most potent first-line oral anti-TB drugs, such as rifampicin and isoniazid [7,15,17,21–24]. When MDR-TB strains acquire additional resistance to any fluoroquinolones and at least one of the second-line injectable anti-TB drugs such as capreomycin, kanamycin, or amikacin, these strains are then referred to as XDR-TB [7,15,17,22–24].

According to a global tuberculosis report in 2013 by the WHO, in 2012, 20% of patients who had been treated for TB had MDR-TB, and the highest prevalence of MDR-TB was observed in eastern Europe and central Asia, where some countries have more than 20% of new TB cases and more than 50% of those previously treated for TB have MDR-TB [2]. The percentage of new TB cases with MDR-TB is shown in Fig. 2. By the end of 2012, It was reported that at least one case each of XDR-TB had been found in 92 countries (Fig. 3), and 9.6% of MDR-TB cases had XDR-TB [2]. Furthermore, only 48% of MDR-TB patients had been successfully treated in the 2010 cohort of detected cases, which is associated with the high mortality rates of MDR-TB [2]. There were approximately 450,000 (range: 300,000–600,000) new cases and 170,000 deaths (range: 100,000–240,000) of MDR-TB worldwide in 2012 [2].

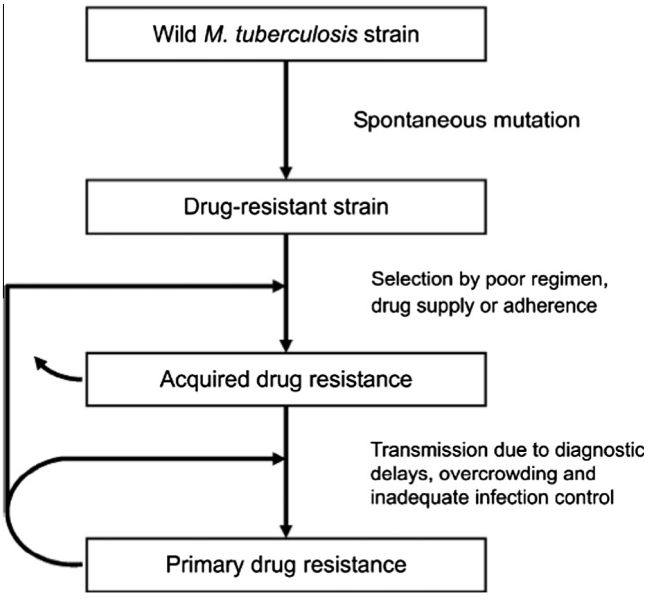

Fig. 1. Steps in the development of drug-resistant tuberculosis. Figure adapted from Ref. [18].

3. Chemotherapy for drug-resistant tuberculosis

Streptomycin which was isolated from *Streptomyces griseus* [25] was reported as the first chemotherapy agent for TB in 1944 [26,27]. At first, it was administered alone, although 80% of patients subsequently developed streptomycin-resistance [28]. This was caused by the streptomycin-resistant mutants which were already present in the TB cavities and they were activated by the streptomycin [29]. Thiacetazone was discovered in 1946 [27], although it was soon discovered to be toxic at high doses [30]. Soon after, it was discovered that treating active TB with a single anti-TB drug had little value, as these treatments led to DR-TB. Therefore, multi-drug therapy emerged as a method to treat TB without inducing drug resistance. For example, *p*-aminosalicylic acid was added to streptomycin and this combined chemotherapy substantially reduced the risk of streptomycin-resistance [31]. In the 1950s, isoniazid and pyrazinamide were introduced and soon after, in the 1960s, ethambutol and rifampin came into use. The introduction times of anti-TB drugs are shown in Table 1 [32]. Aside from fluoroquinolones, it is remarkable and unfortunate that there has been no novel anti-TB drug development in the past 50 years [22,26].

The anti-TB drugs are classified in five groups (Table 2) [17,22,33]. The classification is extremely useful for designing DR-TB treatment regimens. However, drugs in the same group do not necessarily provide the same efficacy or toxicity [33].

Group one; first-line oral agents, includes isoniazid, rifampicin, ethambutol, pyrazinamide, and rifabutin. The treatment for DR-TB begins with any available first-line agent. Next, add one of group two; injectable drugs including the aminoglycosides (streptomycin, kanamycin, and amikacin) and the polypeptides (capreomycin). It is important to use only one of them as they share similar genetic targets [22]. The next treatment step involves the addition of a single fluoroquinolone (levofloxacin, moxifloxacin, or ofloxacin) from group three, although it is also recommended that only one be used, as they all target the *gyr*A gene [34]. Group four; second-line oral bacteriostatic agents, consists of *p*-aminosalicylic acid, cycloserine, terizidone, and the thioamides (ethionamide and prothionamide). It is possible to use one or more of any possible group four drugs if necessary. They should be introduced in the following order: the thioamides, cycloserine, and *p*-aminosalicylic acid. This recommendation is on the basis of their treatment efficacy, adverse effects, and cost [22]. The final step in the treatment regimen for DR-TB is to consider use of the group five agents. Since there is little data regarding their anti-DR-TB efficacy in human beings, group five drugs are not recommended by the WHO for routine use [33]. Therefore, the group five drugs are only used when DR-TB is impossible to deal with using group one-to-four drugs and at least two drugs from the group should be adopted. The recommended order of treatment for group five is: clofazimine, amoxicillin with clavulanate (co-amoxiclav), linezolid, carbapenem, thioacetazone, and then clarithromycin.

4. *In vitro* and *in vivo* photodynamic antimicrobial chemotherapy

Antimicrobial chemotherapy has been investigated by many researchers in previous years. PDT was applied for the treatment of Gram-positive and Gram-negative bacteria. PDT employs photosensitizers that are selectively taken up by tumor cells, and appropriate wavelength of light to treat various cancers [3]. The irradiation produces highly reactive singlet oxygen, which subsequently causes tumor death [3,35]. It has been reported that certain microorganism species are also damaged by PDT. In 1985, Banks et al. reported the *in vitro* photodynamic inactivation of Rose