From Chloroquine to Antineoplastic Drugs? The Story of Antibacterial Quinolones

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Summary

Chemotherapy has not only proved valuable in treating many diseases but the history of discovery of some drugs makes exciting reading. The aim of this article is to outline one such story.

The compound now known as chloroquine (Scheme 1) was first synthesized by H. Andersag at the Bayer laboratories in Elberfeld in 1934. The compound was tested against bird malaria in 1935 and even in four hospitalized psychiatric patients in 1935 or 1936. As a result, chloroquine was abandoned on grounds of its slightly higher toxicity than atabrine in lower animals. However, these facts did not become public knowledge until 1945. Chloroquine was re-discovered in the United States during the course of antimalarial drugs development program in World War II and its high antimalarial activity and therapeutic value were fully appreciated. The drug received its first U.S. trial in man in early 1944 and after extensive clinical trials was introduced into practice in 1947. This early phase of the chloroquine story was admirably described by Coatney[1]. Today, nearly 50 years later, chloroquine is still a mainstream drug in the fight against malaria. Yet the discovery of chloroquine has also strongly influenced antibacterial chemotherapy and may also play a part in antineoplastic therapy in the future, as discussed in the following pages.

Most bacterial infections could be successfully controlled by means of antibiotics and/or sulfonamides in the 1950’s. However, in the course of time, resistant bacterial strains have developed and spread. Therefore, new, more efficient drugs have been sought for by many pharmaceutical companies in their screening programs that have included incredible amount of natural products, as well as synthetic compounds prepared in antibacterial and other projects. This act of looking for a needle in a haystack brought some interesting leads. 7-Chloro-1-ethyl-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (2), which was isolated by Sterling scientists from mother liquors from chloroquine production, was probably the most important one. Formation of the compound was later rationalized by the fact that during the synthesis of (1) by Gould-Jacobs cyclization a small amount of (2) is formed alongside other minor products (Scheme 1).[2]

When (1) was found to be antibacterially active, chemists began to synthesize a series of its derivatives which were examined in the drug screen. The winner in this game of pharmacological roulette was nalidixic acid introduced into practice in 1963 (Nogram®, NegGram®). Nalidixic acid was followed by more useful congeners such as oxolinic acid (Urotrate®, Nidantin®), cinoxacin (Cinobac®, Cinobactin®) and pipemidic acid (Deblaston®, Pipram®). With the exception of Pseudomonades, these drugs are significantly active against Gram-negative bacteria, but inactive against Gram-positives. Their high concentrations in urine after oral administration made them useful for the treatment of urinary tract infections caused by sensitive strains. Rosoxacin (Eradacil®, Winuron®) was intended for the treatment of gonorrhoea, especially cases caused by β-lactamase-producing strains. Rosoxacin and the first fluorine-containing quinolone, flumequine (Apurone®, Uribac®), have good activity against Gram-negative rods and better activity against Gram-
Scheme 2. Selected examples of the classical antibacterial quinolones.

Scheme 3. Fluoroquinolones currently on the market.

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Balofloxacin, Pazufloxacin, Grepafloxacin, Clinafloxacin, DU-6859.

Scheme 4. Fluoroquinolones currently undergoing phase III clinical trials.

Floroxacin®, and sparflloxacin (Sparal®, Zagan®). After Abbott’s withdrawal of temafloxacin (Omniflex®, Temac®, Te-fox®,) in 1992, fluoroquinolones shown in Scheme 3 are available on the therapeutic market, at least in some countries. Preclinical and clinical studies as well as various aspects of the practical use of the mentioned fluoroquinolones have been covered by whole supplementary issues of leading journals. These include ofloxacin[5], ciprofloxacin[6], lomefloxacin[7], fleroxacin[8,9], tosufloxacin[10], levofloxacin[11-13], sparflloxacin[14], and temafloxacin[15].

Besides the mentioned drugs, there are several quinolones in phase III clinical trials that are expected to be launched soon. The current status is well documented in Drug News & Perspectives and even more complex information is available from Trilogy, a CD ROM database published by Prous Science Publishers. Initial information on balofloxacin dihydrat[16] (Chugai), pazufloxacin[17] (Toyama), grepafloxacin[18] (Otsuka), clinafloxacin[19] (Kyorin), and DU-6859[20] (Daichi Seiyaku), drugs currently undergoing phase III clinical trials, is available in the cited monographs.

Several pharmaceutical companies have been interested in the prodrug approach. Compound NAD-441 (Nippon Shin-yaku), currently also in phase III clinical development, is an example of such a prodrug of the corresponding N-unsubstituted compound. The prodrug approach has been applied especially to norfloxacin in order to improve its absorption after oral administration. From a wide range of such produgs norfloxacin succinil (Eminor®[21]) is now preregistered in Italy. Structure of all the mentioned fluoroquinolones in phase III clinical trials are shown in Scheme 4.
Scheme 5. Fluoroquinolones for veterinary use.

Scheme 6. Anticancer topo II inhibitors.

Scheme 7. Quinolone congeners with topo II inhibiting activity.
Several fluoroquinolones have been developed also for veterinary use. Enrofloxacin[22] (Baytril®) developed by Bayer was launched in 1989. Sarafloxacin[23] of Abbott has been submitted for regulatory approval to the FDA and danfloxacin[24] (Advocin®) is undergoing phase II clinical trials at Pfizer. Structures of these compounds are shown in Scheme 5. In spite of the fact that so many quinolones are in therapy or various stages of the development, research into all aspects of this area is continuing. Structure-activity relationships,[3, 25–28] synthesis[3, 29], and mechanism of action[30] of antibacterial quinolones have been recently reviewed.

All quinolones exert their activity through inhibition of DNA gyrase, a bacterial topoisomerase. Since the inhibition of eukaryotic topoisomerase II is a potentially undesirable side effect of the quinolone chemotherapy, there have been several studies that have investigated the activity of clinically used or preclinically tested quinolones against mammalian topoisomerase II (topo II). These studies have shown that quinolones can act quite selectively since DNA gyrase is at least two orders of magnitude more sensitive to many modern fluoroquinolones than the eukaryotic topoisomerases I and II. Nevertheless, some subsets of quinolones have displayed unacceptable cytotoxicity and some of these compounds have been found to be potent inhibitors of topo II.

Mammalian DNA topoisomerase II is essential for cell viability and therefore it is not surprising that this mode of action has been elucidated for several important antineoplastic drugs. These include naturally occurring compounds etoposide (Amizide®, Citodox®, Etopol®, Vepesid®), as well as anthracycline derivatives such as doxorubicin (Adriamycin®, Adriblastin®, Dox®, Rubex®) and daunorubicin (Cerubidine®, Daunoblastin®). Examples of synthetic topo II inhibitors include mitoxanthrone (Misostol®, Noveltrone®, Refador®) and m-AMSA (amsacrine, Amsidine®, Lamasine®). Structures of these drugs are shown in Scheme 6.

Scientists at Pfizer, who discovered a substantial level of topo II inhibiting activity of CP-67,015 (Scheme 7), first recognized that such a combination of a potent activity against prokaryotic and eukaryotic topoisomerase enzymes made such agents attractive leads in the search for potential cancer chemotherapeutics. After Pfizer scientists published their early reports on quinolones possessing topo II inhibitory activity at levels which warranted further consideration as antineoplastic drugs, some pharmaceutical companies started to screen many quinolones that had been eliminated as antibacterial agents for their cytotoxicity. Several subtypes suitable as leads for further development as topo II inhibitors have been discovered. Some examples of such compounds are shown in Scheme 7. Recent development in the field has been recently reviewed.[31]

Antibacterial quinolones represent a well-established class of chemotherapeutic agents. They undoubtedly will play an important role in the chemotherapy of bacterial infections for the next several decades. On the other hand, antineoplastic quinolones represent a new class of perspective drugs with a potential of which has to be established. These compounds possessing both anticancer and antibacterial activity have a particularly promising therapeutic potential due to their ability to reduce the danger of bacterial infections in cancer patients.

References


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