

Can We Discover “Really Safe and Effective” Anticancer Drugs?

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Cancer Burden and Current Knowledge about Cancer and Cancer Chemotherapy

Cancer is a leading killer of human beings worldwide, accounting for 7.6 million deaths (around 13% of all deaths) in 2008 [1]. Overall, an estimated 12.7 million new cancer cases and 7.6 million cancer deaths occurred in 2008, with 56% of new cancer cases and 63% of the cancer deaths occurring in the less developed regions of the world [2]. The most commonly diagnosed cancers worldwide are lung (1.61 million, 12.7% of the total), breast (1.38 million, 10.9%) and colorectal cancers (1.23 million, 9.7%). The most common causes of cancer death are lung cancer (1.38 million, 18.2% of the total), stomach cancer (738,000 deaths, 9.7%) and liver cancer (696,000 deaths, 9.2%) [2]. Although lung cancer is the most common cancer worldwide among men, it ranks second in developed regions (482,000 cases) after prostate cancer (658,000 cases). In women, cervix cancer, the second most common cancer in developing regions (452,000 cases), is only the 10th most common cancer in developed regions (76,000 cases) [3]. World population growth and ageing imply a progressive increase in the cancer burden — 26 million new cases and 17 million cancer deaths are expected in 2030, even if current rates remain unchanged [4]. Therefore, new, safe and effective treatments are clearly needed to curtail these high mortality statistics.

The four major modules of cancer treatment include surgery, radiation, chemotherapy and immunotherapy [5]. However, these therapies are only successful when the cancer is detected at an early stage, or limited to certain types of cancer (e.g., leukemia). Due to the inability of detecting cancer at an early stage, most patients present in the advanced stage with extensive local infiltration and metastasis. For advanced tumors, in particular those tumors developed from epithelial tissues such as lung, colon, breast, prostate and pancreas, these therapies are less successful.

Chemotherapy represents one of the major means for cancer treatment, which aims to kill tumor cells or to inhibit their proliferation while preserving the normal cells in the body [5]. Chemotherapeutic agents generally have a narrow margin of safety, and are used in combination usually given at a maximum tolerated dose to achieve maximum cancer cell killing [6]. They kill tumor cells by direct cytotoxicity, or activating host immune response, inhibiting the proliferation processes of tumor cells, and inducing apoptosis [7]. For most anticancer drugs, there is a large inter-individual variability in their pharmacokinetics and this can result in unpredictable toxicity and variable antitumor effects [8]. However, most patients do not respond to these drugs and they often experience severe adverse effects such as severe diarrhea and loss of hairs. The primary reason for this is because the drug kills both normal and tumor cells and drug levels within tumor cells are too low. Drug resistance and dose-limiting toxicities are the major problems for the success of cancer chemotherapy [9].

Why does Cancer Chemotherapy often Fail?

The discovery of “really effective” anticancer drugs remains a highly challenging task for cancer pharmacologists and medicinal

chemists [10]. Despite the wide use of approximately 140 anticancer drugs (mostly cytotoxic agents and biologically targeted therapeutic products) in clinical settings, we cannot alter the lethal nature of cancer, with only incremental overall improvements in therapeutic outcomes at the price of considerable host toxicities. To date, anticancer drugs have only given a very low success rate (~5%) in clinical development and application which is significantly lower than drugs in other areas [11].

The reasons for the failure of saving patients’ life using currently available anticancer drugs are multifaceted, which are probably associated with a number of factors associated with the drugs and patients. The poor prognosis of almost all solid tumors forces us to accelerate the development of anticancer drugs. To compress the development timelines and establish the feasibility of assays for target modulation in human samples, the Food and Drug Administration has incorporated a Phase “0” trial platform which allows accelerated evaluation of biomarkers for drug effects and pharmacokinetic behaviors of the novel anticancer drugs [12]. Recent changes to non-clinical cancer guidelines by FDA offer a better opportunity to expedite the translation of new anticancer drugs into the clinic [13]. Although new and optimal drug-discovery programs may integrate the different stages of the discovery and development process into a single coherent operation, the clinical significance is yet to be confirmed.

Is Something Wrong with our Current Knowledge and Models for Cancer?

The apparently disappointing results in clinical use of almost all oncology compounds and the fact that cancer disease is still fatal prompt a critical question: is something wrong with our knowledge and models for cancer? The answer is “yes”. It is unlikely to develop “safe and effective” anticancer drugs based on our existing knowledge about cancer and models for oncology compound development [14,15]. Before the basic questions about cancer (e.g. how does the cancer cellular signaling network run? How can we eradicate cancer stem cells? Are the models used for oncology compound development representative of the tumor in its native state? How do epigenetic factors regulate cancer cell growth?) I have not been addressed due to perceptual and technical limitations; cancer remains a fatal disease.

Should we make a Revolutionary Change of our Knowledge about Cancer?

To win the war against cancer, a revolutionary change of our

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knowledge about cancer is certainly needed. By using emerging techniques and platforms such as computational medicinal chemistry and systems biology/pharmacology, the detailed regulation mechanisms, epigenetic and genetic information and signaling network for the growth, proliferation and metastasis of cancer cells may be revealed and thus novel strategies to eradicate cancer cells from the body, overcome tumor resistance and discover "magic" drugs that kills cancer cells only without affecting the normal cells becomes possible [16-18]. With a full understanding of the biological behaviors of cancer growth and metastasis and proper application of such knowledge in anticancer drug development, it is likely to cure cancer like for infectious diseases.

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