Theories of Cancer Chemotherapy

There are several hypotheses that are generally well known as basic theories of cancer chemotherapy; only the main points are described below.

The Skipper-Schabel-Wilcox model was derived from the results of experiments using mouse leukemia L-1210 cells and is applicable to the treatment of leukemia in humans [5]. In this model, it is hypothesized that tumor growth is exponential and thus anticancer agents kill tumor cells in a log-kill manner. A certain dose of a drug can kill a fixed percentage of cells. For example, assuming that a drug can kill 99.99% of target tumor cells, the cell number decreases from $10^9$ to $10^4$. With the same dose of the drug, the cell number decreases from $10^5$ to $10^1$. Therefore, unless the total number of tumor cells is $10^4$ or less, the number of tumor cells never becomes 0; in other words, the tumor can never be completely eliminated.

The Gompertzian model was developed by expanding the theory of the Skipper-Schabel-Wilcox model to reflect the growth style of a solid tumor [6]. In this model, it is hypothesized that a tumor growth profile can be expressed by an exponential curve when it is plotted along a temporal axis with equal intervals. A tumor grows slowly at the beginning and then rapidly changes to fast-growing. Subsequently, when the tumor grows large enough, its GF becomes low and accordingly its growth potency also declines. In other words, the tumor growth profiles can be represented as an S-shaped curve. In addition, as the tumor grows larger and its GF becomes low, its heterogeneity becomes high, and drug sensitivity becomes low. Treatment failure in cancer chemotherapy is most likely attributed to the fact that the total number of target tumor cells is too large or that the absolute amount of drug is not sufficient.

The Norton-Simon hypothesis was developed by further advancing the theory of the Gompertzian model [7,8]. In this model, the tumor growth profiles can be represented as an S-shaped curve and the change in the tumor cell number following a treatment with anticancer agents or a radiation therapy can be represented as a mirror image of the growth curve. Thus, the tumor cyto reductive rate is low when the number of target tumor cells is very small or large, and tumor size can be drastically reduced when the cell number is intermediate. This can account for the fact that it is difficult to completely eradicate tumor cells and to obtain a survival benefit even after the size of the tumor has been reduced (i.e., primary therapeutic effects can be obtained) by chemotherapy.
The Goldie-Coldman hypothesis was developed by expanding Delbruck Luria’s theory regarding bacterial resistance to virus [9,10]. This is the most important theory related to the treatment of drug-resistant cancer. In theory, a drug-resistant cell appears in every \(10^3\) to \(10^6\) cells. This is much less than the cell number when tumor cells are found in clinical situations, generally \(10^9\) when \(\geq 10^3\) drug-resistant cells are supposed to exist. For this reason, even if complete response (CR) can be obtained by chemotherapy, it is possible that drug resistant cells that escape treatment and remain viable would grow rapidly afterward. In this case, complete cure is difficult. Therefore, there is a concept that tumor cells should be eradicated by concomitant use of multiple effective drugs as early as possible before the resistance-acquired cells build up in the tumor. However, due to possible adverse events, treatment by concomitant use of many agents is not practical. In theory, a permanent cure of a tumor can be achieved by treating with several cycles alternating effective multidrug regimens (i.e., regimen A and regimen B) which do not have cross resistance (ABABAB). However, it is difficult to precisely put this theory into practice in a clinical setting. Currently the effectiveness of this alternating chemotherapy has not been proven, although clinical trials in patients with small cell lung cancer, breast cancer, and Hodgkin’s disease have utilized this treatment method [11].

Day [12] proposed the worst-drug rule, which came from the Goldie-Coldman hypothesis. According to this rule, when there are two regimens (A and B) and A is more effective than B, regimen B should be applied first to reduce the size of the tumor. Then when the number of tumor cells has decreased making conditions more favorable for chemotherapy, the more potent regimen A should be applied to eradicate the drug resistant cells. However, in clinical practice, drugs with the most potential to be effective are likely to be administered first in many cases; the concept of starting with drugs with less potential for efficacy is generally not acceptable to clinicians.

Norton expanded on the Norton-Simon hypothesis and demonstrated by computer model that it is difficult to eradicate tumor cells by alternating administration of two agents when there are two types of drug-resistant cells. He focused on a heterogeneous cell population and proposed a therapeutic strategy to treat a cell population that is in a growth phase (high sensitivity) first, and then treat the other cell population (slow growth and resistant) second. In this strategy, an effective regimen A is repeated for several cycles followed by the same for regimen B (AAA…BBB…etc.). In contrast to alternating chemotherapy (ABAB…), the dose-intensity of each regimen can be determined in this method [13]. Clinical applications of this method, however, have resulted in contrasting outcomes. There have been data reported both supporting and refuting the effectiveness of this method [14,15]. Practice of this theory requires several effective agents and at least two effective regimens that do not have cross resistance. However, effective agents are not sufficiently available under the present set of circumstances, which is the biggest obstacle preventing precise practice of the theory.


