Journal of Drug Metabolism and Toxicology

Kogashiwa and Kohno, J Drug Metab Toxicol 2013, 4:1
DOI: 10.4172/2157-7609.1000141

Commentary Open Access

Combination Chemotherapy for Solid Tumors in Head and Neck

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Abstract

Purpose: The basic idea of combination chemotherapy is to eradicate tumor cells through potent therapy before the appearance of resistant cells or an elevation in the number of the resistant cells. This article explores the use of combination chemotherapy in the treatment of solid tumors in head and neck.

Method: The efficacy of chemotherapy for head and neck tumors is specifically reviewed.

Results: Several hypotheses are generally well known and accepted as basic theories in cancer chemotherapy, and researchers have developed effective combination chemotherapy regimens based on these theories. Chemoradiotherapy was initially developed to regulate the local tumor through radiation and control distant metastases through chemotherapy. The purpose of adjuvant chemotherapy is to treat latent tumor cells that cannot be seen macroscopically after completion of first-line therapy. Continuous administration of a small dosage is a new concept that has recently been proposed to replace the conventional concept of total cell-killing.

Conclusion: This article examines the use of combination chemotherapy in the treatment of solid tumors and reviews the efficacy of chemotherapy, which should be understood by head and neck surgeons.

Keywords: Adjuvant; Induction chemotherapy; Chemoradiotherapy; Continuous administration

Introduction

In cancer chemotherapy, a group of tumor cells can become targets of the therapy only after they are histologically and conclusively diagnosed as a tumor. Generally, at the stage of diagnosis, the number of the tumor cells already exceeds 1×109 (1 g), the cell growth curve stays on the plateau [1], and the cell population is highly heterogeneous. Thus, therapeutic effects of chemotherapy can no longer be expected in these tumor cells since their growth fraction (GF) is low. Accordingly, in order to achieve a therapeutic effect, potent therapy would be required due to the tumor having advanced to a more intractable state.

Some types of cancers, such as chorionic carcinoma and Burkitt's lymphoma, can be cured by treatment with a single agent, although these are extremely exceptional cases. It is impossible to uniformly kill a group of cells with high heterogeneity and thus difficult to obtain a good outcome through administration of a single anticancer agent because the group of cells is likely to comprise cells that are responsive to the treatment as well as those that are resistant. As a result, therapy combining multiple agents that have different mechanisms of action has evolved, i.e., combination chemotherapy. The goal of combination chemotherapy is to eradicate tumor cells through potent therapy before the appearance of resistant cells or an elevation in the number of the resistant cells.

Evaluation of Combination Chemotherapy

Treatment with multiple agents would not have any benefit if the drugs used have antagonistic effects and thereby cancel each other out. Ideally, multiple agents must work synergistically. Therefore, it is necessary to evaluate (through analysis of laboratory-level data) whether a specific combination would work well in clinical situations prior to clinical application.

One of the methods used to evaluate the effectiveness of multiple drug-based treatments is the fractional product method. In this method, when agents A and B (both of which can kill 50% of target cells) are concomitantly used, their combination use is considered effective only if the survival fraction of the treated cells is ≤ 25% (1/2×1/2=1/4); in other words, if ≥ 75% of the cells are killed. However, this method can be used to evaluate only a single ratio of the combination of the two agents.

Steel and Peckham modified the fractional product method to devise an isobologram [2]. Using an isobologram, the combination of two agents at any ratio can be evaluated and determined to be synergistic or antagonistic. Therefore, the efficacy of a combination therapy can be evaluated easily and objectively at a laboratory level.

Other methods are also being used to evaluate multi agent cancer chemotherapy regimens. Chou and Talalay reported median effect plot analysis, a computer-based analysis [3]. The summation dose intensity (SDI) is another method that represents a summation of the objective evaluation of factors in clinical situations, such as efficacy rate, dose, adverse reactions, and others, of agents in combination use [4].

Hypotheses

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

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Received November 30, 2012; **Accepted** January 21, 2013; **Published** February 14, 2013

Citation: Kogashiwa Y, Kohno N (2013) Combination Chemotherapy for Solid Tumors in Head and Neck. J Drug Metab Toxicol 4: 141. doi:10.4172/2157-7609.1000141

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 109 to 104. With the same dose of the drug, the cell number decreases from 105 to 101. Therefore, unless the total number of tumor cells is 104 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 103 to 106 cells. This is much less than the cell number when tumor cells are found in clinical situations, generally 109 when ≥ 103 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.

Other considerations

In addition to the theories, the following matters should be considered.

Biochemical theoretical rationale: Important substances such as nucleic acid, which constitute a cell, utilize several alternative metabolic pathways. Accordingly, it is necessary to inhibit all of these pathways in order to completely kill tumor cells. To that end, Sartorelli proposed combination chemotherapy using several agents that inhibit different sites of metabolic pathways.

Recruitment: Upon reduction of the absolute number of tumor cells (which can be achieved by surgery, radiation therapy, and/or non-cell-cycle-specific chemotherapy), the relative blood flow volume of the remaining tumor cells could be increased. This would lead resting cells in a G0/G1 phase to become dividing cells and thereby increase the GF of the tumor. Tumor sensitivity to cell-cycle-specific agents would increase and combination therapy could be effective. This concept has been verified experimentally but not in a clinical setting [1].

Synchronization: Tumor cells proliferate by repeating their cell cycle. Among anticancer agents, DNA synthesis and mitosis inhibitors arrest cell turnover and, in theory, synchronize tumor cells at a certain cell cycle. During cell synchronization, tumor cells can be more effectively killed by exposure to agents to which they are sensitive. Therefore, this is one of the effective ways in which anticancer agents can be effective against a highly heterogeneous cell population. However, it is difficult to obtain synchronization in a solid tumor compared with *in vitro* cultured cells. In addition, even if synchronization is achieved, it is possible that not only tumor cells but also normal cells are synchronized, which is likely to result in severe adverse reactions. Because of these problems, successful clinical applications of this method have not been reported and achieving success with synchronization is a challenge for the future [16].

Pharmacological theoretical rational

The fundamental matters in the theory of combination therapy can be summarized as follows:

1. Drugs that are effective as sole regimens should be used. Drugs with a high CR rate should be selected rather than those with a high partial response (PR) rate.
2. Drugs with different mechanisms of action should be used. In addition, it is better to choose those with different mechanisms of developing drug resistance (Table 1) [17,18].
3. Drugs that cause different adverse events, especially those with different dose-limiting toxicities, should be used.
4. The full dose should be used for each drug.
5. When drugs with overlapping adverse drug events are used concomitantly, adjustment of their doses is necessary.
6. Dosing intervals should be minimized as much as possible while providing normal cells a sufficient period of time to recover from the damage caused by anticancer agents.

Design of the administration schedule

A favorable administration schedule can be defined as one that achieves maximum therapeutic effect with minimal adverse events. Agents that have characteristics of dose dependency, such as alkylating agents and anticancer antibiotics, are classified as cycle-specific agents. Those, that have characteristics of time dependency, such as antimetabolic agents and plant alkaloids, are classified as phase-specific agents. In cancer chemotherapy, the drug characteristics should be taken into consideration. For example, the cytotoxic effect of an antimetabolic agent, 5-fluorouracil (5-FU), can be markedly enhanced by increasing the duration of cellular exposure to the drug. In fact, in combination therapy with cisplatin (CDDP) for patients with head and neck cancer, the response rate (RR) dramatically improved from 20% to 72% by switching administration method of 5-FU from an intravenous bolus injection to a continuous infusion [19].

On the other hand, a therapeutic effect on solid tumors can only be obtained after the drugs penetrate the feeding vessel, infiltrate to deep parts of the tumor mass, and contact the target tumor cells [20]. Drug penetration is influenced by environmental factors such as intercellular adhesion strength and pH, and drug-related factors such as molecular weight and lipophilicity of the drug. In terms of these factors, 5-FU and CDDP have favorable physicochemical properties. Based on these facts, the following points are important when designing an administration schedule.

1. Phase-specific agents are only effective on cells with a high GF. Thus, it is reasonable to use cycle-specific agents first. In particular, agents with high penetration properties (e.g., CDDP) are suitable for treating solid tumors.
2. Phase-specific agents with short half-lives should be given by low-dose fractionated administration or continuous infusion.
3. Cycle-specific agents should be given by high-dose intermittent administration.
4. When tumor cells become resistant to an agent, another agent that is unlikely to exhibit cross resistance with the first one should be selected (Table 1).
5. Agents should be administered repeatedly as long as they are effective.
6. Drug-free intervals should be provided to allow normal cells to recover. Since recovery of bone marrow takes generally 2 to 3 weeks, the drug-free period should be at least that long.

Drug-drug interaction

Concomitant use of a modulator and an effector can alter the pharmacokinetics of the effector and enhance its activity, leading to a synergistic effect. Greater understanding of this mechanism could lead to more effective combination therapy. To date, the mechanisms of action of several combinations for biochemical modulation have been clarified; representatives of such combinations are described below.

Methotrexate (MTX)+5-FU: MTX decreases the amount of reduced folate (folic acid) resulting in an elevation of intracellular phosphoribosyl-1-pyrophosphate (PRPP). This leads to more active conversion of 5-FU to 5-fluoro-2'-deoxyuridin 5-monophosphate (FdUMP), which inhibits DNA synthesis, and to 5-fluorouridine 5'-triphosphate (FUTP), which is incorporated into RNA and causes damage; thereby, the effect of 5-FU can be enhanced by MTX [21].

CDDP+5-FU: CDDP inhibits DNA synthesis through its direct action on DNA. In addition, CDDP works as a modulator of 5-FU. CDDP acts on and disrupts the cell membrane and inhibits intracellular uptake of methionine, which prompts the cells to synthesize it. Reduced folate is produced as a by-product of this process resulting in elevated levels of intracellular folate. Upon binding of FdUMP (5-FU active metabolite) to thymidylate synthase (TS), DNA synthesis is inhibited and an anticancer effect can be achieved. The concomitant presence of a high level of folate induces strong binding of the FdUMP and TS, and enhances the anticancer activity of 5-FU. Therefore, CDDP enhances the activity of 5-FU. In fact, *in vitro* experiments using cultured ovary cancer cells demonstrated that more cytotoxic effect could be obtained by treating with CDDP first followed by 5-FU rather than the reverse order [22]. In contrast, Esaki et al. demonstrated that administration of 5-FU followed by CDDP was the more effective order based on their animal experiments using tongue cancer-derived cells. According to their explanation, this was probably because 5-FU lowered DNA synthesis by inhibiting the restoration of DNA from its cross-link with CDDP [23]. As to administration schedule for these two drugs, one group insisted that 5-FU should be administered first [24], while another group concluded that the enhancing effects to be obtained in different administration schedule depended on the types of target tumor, based on their animal experiments.

CDDP+Doxorubicin (DXR): Chemotherapeutic drugs are only effective once they have penetrated the tumor cells deep within the mass. DXR is effective in monolayer-cultured cells, but less effective

Topoisomerase I inhibitors (CPT-11, NB-506)	Topoisomerase II inhibitors (ETP, DXR)
Other drugs (CDDP, VCR, 5-FU)	MDR drugs (DXR, ETP, VCR)
Alkylating agents (CDDP, CPA)	NB-506
Topoisomerase II inhibitors-Non P-gPmdr (ETP)	CDDP, Paclitaxel, MMC
CDDP	Paclitaxel, DXR, VCR, CPT-11
Paclitaxel	VCR, CDDP

Abbreviations: CPT-11, Irinotecan; NB-506, glucosyl derivative of indolo-carbazole; ETP, Etoposide; DXR, Doxorubicin; CDDP, Cisplatin; VCR, Vincristine; 5-FU, 5-fluorouracil; CPA, Cyclophosphamide ; MMC, Mitomycin C

Table 1: The drugs which exhibit cross resistance each other.

in multicellular tumor spheroids (MTS), which is a model for solid tumors. Therefore, in its concomitant use with CDDP (which has a high penetration property) optimum therapeutic effect can be achieved by first treating with CDDP followed by DXR 1 hour later. A possible mechanism of this augmented efficacy is that CDDP makes a path in intercellular spaces between neighboring cells through which DXR can penetrate more efficiently [20].

MTX+Leucovorin (LV): MTX decreases the level of reduced folate which is essential to DNA synthesis by inhibition of dihydrofolatereductase (DHFR). In order to reduce adverse events, LV is added to supplement DHFR which is suppressed by MTX administration. Through this combination, the MTX dose can be increased (dose escalation) and drug resistance avoided. Cells acquire resistance to MTX by inhibition of its intracellular uptake via active transport in the cell membrane and/or by lowered affinity of MTX to DHFR through up-regulation of the DHFR gene in the cells. MTX can enter the intracellular space according to a concentration gradient when a high concentration of MTX is used, rather than by active transport in the cell membrane. Furthermore, the lowered affinity to DHFR can be overcome when the combination of MTX is kept high for a long period. In clinical applications, the combination of MTX and LV has been proven effective in acute lymphatic leukemia and osteosarcoma. However, it is not as effective in other cancers since tumor cells are also rescued by LV in addition to normal cells. For this reason, the combination of MTX and LV has not been shown to have an obvious advantage over MTX alone [25].

FU+LV: LV inhibits DNA synthesis by forming a ternary complex among its active metabolite [5,10] methlenetetrahydrofolate (CH2THF)], an active metabolite of 5-FU (FdUMP), and TS in tumor cells. The inhibitory activity of this combination is much higher than that of 5-FU alone. This combination has been proven to be effective in clinical situations. To date, 10 controlled studies of 5-FU+LV in patients with colorectal cancer have been reported. In 8 of them, the combination of 5-FU and LV showed a higher RR than 5-FU alone and, in one study, the RR and survival period were significantly higher in the patients receiving the combination over those administered 5-FU alone [26,27].

Alkylating agents/CDDP+Buthioninesulfoximine (BSO): Glutathione (GSH) has a cytoprotective property; therefore, when intracellular GSH is increased, cells acquire resistance to anticancer drugs. BSO inhibits GSH synthesis and thereby can enhance the effects of alkylating agents, platinum-containing agents, and radiation when used concomitantly [28]. Clinically, the administration of BSO does not cause any adverse effects even at the dose by which the GSH level is reduced to 10% of that before BSO administration; combinational effects can be expected [29].

Verapamil+DXR/Vincristine(VCR): Verapamil (calcium channel blocker) prevents drug efflux from the intracellular to the extracellular space of tumor cells by inhibiting P-glycoprotein. By preventing this efflux of anticancer agents into the extracellular space, high concentrations of the agents are maintained in the target cells, thereby maintaining the therapeutic effects of the anticancer agents. This combination has been proven effective in a laboratory-level study and has been gaining attention as a possible means to avoid multidrug resistance related to P-glycoprotein [30].

CDDP/Docetaxel (DOC)/DXR+Cetuximab: Cetuximab binds to epithelial growth factor (EGF) receptor with affinity comparable to the natural ligand and competes with ligand binding and receptor tyrosine kinase activation [31-33]. It also dimerizes and downregulates the EGF receptor, which prevents further receptor binding and activation by the ligands [34]. Several studies have suggested that interruption of the EGF receptor-ligand autocrine pathway by cetuximab results in disturbance of the cell-cycle progression due to a G1-phase arrest [35-37], which subsequently inhibits the growth of malignant tumor cells. Although the mechanisms accounting for the enhanced antitumor effects of combination treatment are under investigation, preclinical and clinical studies also suggest that blockade of EGFR allows augmentation of antitumor activities when combined with CDDP, DOC, or DXR [34,38,39].

Dosage selection based on toxicity

If the dosage of anticancer agents is not sufficient, a therapeutic effect cannot be expected. The major cause of treatment failure in cancer chemotherapy is that too low of a dose is selected due to concern about adverse events. In many cases, the dose response curves of anticancer drugs show a very steep slope. Generally, the relationship between the dosage of drugs and the number of killed cells is represented as a linear log (exponential) curve. It shows the effect of 5-FU on larynx cancer-derived Hep-2 cells. A two-fold increase of the dose of 5-FU resulted in more than a 10-fold increase in the number of affected tumor cells. This indicates that a small change to the dose lead to a substantial improvement of RR. Taken together, these findings suggest that it is important to select the dosage with which adverse drug events can be kept at a minimum while still obtaining the optimum effect.

In clinical practice, dose must be reduced when adverse events occur, which prevents uniform dosages because different drugs have different influences on adverse reactions. For example, bleomycin (BLM) is less likely to cause bone marrow suppression. Therefore, even when bone marrow damage is caused by other agents, BLM can be used with relative safety.

Chemoradiotherapy

The main purpose of cancer therapy is to prolong patient survival. In addition, chemoradiotherapy aims to improve local control of the tumor size and rate of growth and preserving organ function. In patients with advanced head and neck cancer, radical surgery may cause eating disorder and dysarthria. If a CR is achieved by chemoradiotherapy, radical surgery can be avoided, which is highly advantageous in terms of preserving function. Therefore, successful applications of this method are expected in terms of functional and morphological preservation.

Chemoradiotherapy is currently the most effective treatment for patients with head and neck squamous cell carcinoma (HNSCC). Pignon et al. showed that chemotherapy was more effective in the groups receiving concomitant radiotherapy than in the induction or adjuvant groups in their meta-analysis on 93 randomized trials and 17,346 patients (performed between 1965 and 2000) [40]. Both direct and indirect comparisons showed a more pronounced benefit of the concurrent chemotherapy as compared to induction chemotherapy. For the 50 concomitant trials, the absolute benefit was 6.5% at 5 years for overall survival, compared to 2.4% at 5 years for the 31 induction trials. Munro performed a bibliographical analysis of controlled studies (performed between 1963 and 1993) on chemotherapy against head and neck cancer. Among the more than 150 studies reported so far, there were 54 where survival periods were clearly recorded and control groups that did not receive chemotherapy were included. Based on his detailed analyses of these 54 studies, the outcomes of patients receiving chemoradiotherapy were better than those in the control groups. Specifically, the survival (compared to control groups) was

prolonged by 3.7% and 12.1% by preoperative chemotherapy and chemoradiotherapy (single agent plus radiation), respectively. CDDP and 5-FU were the most effective; survival was prolonged by 10.1% in patients treated with these drugs [41]. Similarly, El-sayed and Nelson reported the effectiveness of the chemoradiotherapy [42].

Recently, Vermorken reported that induction chemotherapy with the addition of DOC significantly improved progression-free survival in patients with unresectable HNSCC as compared with the standard regimen of CDDP and 5-FU [43]. Patients were randomly assigned to receive TPF (DOC and CDDP, Day 1; 5-FU continuous infusion, Days 1 to 5) or PF (CDDP, 5-FU) every 3 weeks for 4 cycles followed by radiotherapy. At a median follow-up of 32.5 months, the median progression-free survival was 11.0 months in the TPF group and 8.2 months in the PF group (p=0.007).

Historically, the combination of anticancer agents and radiation therapy has been used for treating pathological lesions of the skin and mucosa; agents used in these cases included DXR and actinomycin D. At present, agents that are confirmed to be effective and have received good clinical evaluations include hydroxyl urea for cervical cancer, 5-FU for head and neck cancer, gastric cancer, and bladder cancer, CDDP for head and neck cancer, lung cancer, bladder cancer, and gynecological cancers, and BLM for head and neck cancer [44-51].

Chemoradiotherapy was initially developed to regulate the tumor locally through radiation and control distant metastases through chemotherapy. To improve the local control of a radiation-treated field by chemotherapy was a secondary aim. Therefore, it was reasonable to use full doses for both chemotherapeutic agents and radiation and such regimens have been designed and implemented. Adverse events, especially mucosal damage in the treated field (diarrhea, stomatitis, etc.) are a problem with these regimens. Because of adverse events, it is difficult to complete a treatment plan when a full dose of anticancer agents is used; this necessitates reduction of irradiation level.

The mechanism by which platinum-containing agents and radiation enhance one another is thought to be that platinum-containing agents kill hypoxic cells which are resistant to radiation or the platinum-containing agents prevent the recovery of irradiated cells.

Adjuvant chemotherapy

The purpose of adjuvant chemotherapy is treatment for latent tumor cells whose presence cannot be found macroscopically after completion of a first-line therapy. Since this therapy is targeted to an exponentially growing cell population in which the total number of tumor cells is low, if any, and the GF is high, chemotherapy can be expected to be the most effective method [52]. Furthermore, based on the results of basic experiments, the anticancer effect of drugs is known to be correlated with the GF at the time of drug administration. Nonetheless, it is difficult to obtain a good clinical outcome in many cases. This is probably due to a problem with the method of administration. Adjuvant chemotherapy is a preventive treatment for latent cancer lesions so the dosage is usually adjusted to reduce the burden on patients as much as possible. For this reason, the amount of drug is generally not enough to eradicate tumor cells, which results in reduced effectiveness as well as fewer adverse events. Therefore, if adjuvant chemotherapy is going to be administered, a full dose should be given. An administration period of 6 to 8 cycles over 2 years would be a common schedule. Hudis et al. [53] showed that a good outcome could be achieved by a regimen in which full doses of DXR, paclitaxel, and cyclophosphamide were administered for 9 cycles after surgery in patients with advanced breast cancer.

Reinfuss et al. [54] reported that survival could not be prolonged by adjuvant therapy with MTX following completion of a first-line therapy in patients with nasopharyngeal cancer. On the other hand, Rahima et al. demonstrated that 3-year survival rates were 83% and 61% in patients treated by adjuvant chemotherapy with CDDP, MTX, and BLM and those without chemotherapy (control group), respectively. They also observed a reduction of distant metastases in patients treated by this combination of adjuvant chemotherapy [55]. Al-Sarraf et al. [56] showed that, in 150 patients with advanced nasopharyngeal cancer (Stage III or IV) who had received chemoradiotherapy with CDDP (100 mg/m^2) and radiation (70 Gy), median progression-free survival was significantly prolonged in those treated by adjuvant chemotherapy with CDDP and 5-FU (52 months)than those without chemotherapy (13 months) (p<0.0001) [56]. This suggests the necessity of full-dose adjuvant chemotherapy. In addition it is important that doctors and patients both understand adjuvant therapy to minimize drop-out.

Ideally, an outpatient regimen that has a strong impact is desired. An outpatient regimen combining a low dose of CDDP and a UFT internal agent is one of the regimens that meet such needs at the present moment. The UFT internal agent is a 5-FU analogue composed of uracil and Futraful (a pro-drug of 5-FU) at a molar ratio of 1 to 4, respectively, where uracil is added to enhance the antitumor effect by suppressing the degradation of 5-FU but not its phosphorylation. The combination of S-1 (a drug which is composed of Futraful, 5-chloro-2,4-dihydroxypyridine which inhibits a degrading enzyme of 5-FU, and potassium oxonate which alleviates 5-FU toxicity to the gastrointestinal tract at a molar ratio of 1 to 0.4 to 1, respectively) and platinum could also be a regimen that has potential for the future use [57].

Continuous administration of small dosages

Cancer therapy should be performed for as long as possible while minimizing adverse events. Cancer therapy should aim at prolonging survival and maintaining QOL while retarding the progression of cancer. This is a new concept that has recently been proposed to replace the conventional concept of "total cell killing". Although chemotherapy that aims at the total cell killing could be effective in part, the therapy must be discontinued in many cases due to treatment-associated adverse events and, consequently, no therapeutic effects are obtained. The new concept is a next generation cancer chemotherapy which arose based on such failures. In other words, the new concept is to purposely reduce adverse events and prolong survival by a long drawn-out type of administration as the main strategy [for example, combination of CDDP (2 to 3 mg/m^2 on Days 1-5) and 5-FU (200 to 300 mg/m^2 on Days 1-7) for a total of 4-6 weeks]. Studies have reported that chemotherapy for unresectable or recurrent cancer after surgery for advanced gastric cancer achieves a significantly longer survival time than best supportive care. The main agent used was S-1 [58-60]. In clinical practice, the recommended dosage regimen is 4 weeks of daily administration followed by 2 weeks of withdrawal, frequently causes bone marrow suppression and non-hematological toxicities such as skin and digestive system disorders [61]. 5-FU acts on the S phase of the cell cycle and inhibits DNA synthesis which suppresses tumor cell proliferation. Lipkin et al. [62] in 1963 and Clarkson et al. [63] in 1965 reported that normal cells and tumor cells have different cell cycles (0.5 to 1.5 days and 5 to 7 days, respectively). Shirasaka et al. [64] hypothesized that when 5-FU is given on alternate days, tumor cells are exposed to 5-FU at regular intervals, resulting in sufficient antitumor effectiveness. However, because of their shorter cell cycle, normal cells are only exposed to 5-FU every other day, thereby reducing toxicity [64,65]. On the basis of this method, alternate-day treatment with S-1

in patients with gastric cancer was studied and it was reported that the treatment may have milder adverse events without compromising therapeutic effectiveness [66-68].

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Citation: Kogashiwa Y, Kohno N (2013) Combination Chemotherapy for Solid Tumors in Head and Neck. J Drug Metab Toxicol 4: 141. doi:10.4172/2157-7609.1000141