Progress in Chemotherapy of Malignant Bone Tumors

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Abstract: In the past 30 years, great progress has been achieved in the treatment of malignant bone tumors, which must be significantly attributed to the application and gradual improvement of chemotherapy, especially the appearance of neo-adjuvant chemotherapy concept and the application of its rules. Represented by osteosarcoma and Ewing's sarcoma, malignant bone tumors mainly relied on amputation, local wide resection and sufficient radiation therapy before the appearance of chemotherapy, and these conventional therapies often resulted in the lifelong disability of patients and very high local recurrence rate. Moreover, the 5-year survival rate was less than 20%. However, neo-adjuvant chemotherapy brings the hope for patients with malignant bone tumors to keep their extremities and functions, and the 5-year survival rate in foreign countries exceeds 80% [1], while the 5-year survival rate reported in China also reached 50%~60% [2]. The principles and methods of tumor chemotherapy are concluded from numerous clinical practices, which is divided in the following stages: single-drug adjuvant chemotherapy; multiple-drug combination chemotherapy and chemotherapeutic application of maximum tolerated dose (dose-intensity); application of (adjuvant) chemotherapy during clinical metastasis of disease; application of (neo-adjuvant) chemotherapy prior to other treatment.

I. Single-drug Adjuvant Chemotherapy

Osteosarcoma is a relatively drug-resistant tumor, so single-drug chemotherapy cannot achieve the satisfying effect, and only a few drugs could achieve the effectiveness of more than 15%, but most drugs are only partially effective. At present, the drugs for osteosarcoma chemotherapy mainly include Adrimycin (ADM), Cisplatin (CDP), High-Dose Methotrexate (HD-MTX), Vincristine (VCR), Bleomicyn, Cyclophosphamide (CTX), Dactinomycin, and Ifosfamide (IFO), etc. Table 1 listed the therapeutic effect of single-drug chemotherapy against osteosarcoma. ADM (Epirubicin hydrochloride: Pharmacia Corp.; Pirarubicin: Shenzhen Main Luck Pharmaceuticals Inc.) and MTX are the main drugs for osteosarcoma chemotherapy. The therapeutic effect of drugs depends on the dose, so higher dose may improve the effectiveness. The application of CTX in the treatment of Ewing's sarcoma was first reported in the 1960s, but CTX is still the most effective drug for single-drug chemotherapy today. The reaction rate in the Stage II research (entire or partial reaction) exceeded 40%. In the 1970s, ADM appeared very effective in the Stage II experiment, and its reaction rate went beyond 40%. In the mid-1980s, Etoposide (Vp-16) was used as a single drug, but the reaction rate was less than 30%. However, IFO achieved the reaction rate of more than 30%. High-dose melphalan realized the reaction rate of around 80% in the treatment of Ewing's sarcoma. All the above drugs have now been regarded as the most effective drugs for therapy in the clinical practices [3].

II. Multiple-Drug Combination Chemotherapy and Chemotherapy with Maximum Tolerated Dose (Dose-Intensity)

To eliminate the limitation that single-drug chemotherapy easily causes the drug resistance of

tumor cells, combination chemotherapy with several drugs has been developed constantly. For instance, osteosarcoma is treated with the combination chemotherapy relied mainly on HD-MTX, CDP, ADM, and IFO, while the combination chemotherapy using VCR, ADM, Actinomycin D (ACD), CTX and Vp-16 is used to treat Ewing's sarcoma. The principle of combination chemotherapy is to combine the drugs with therapeutic effect on tumor for realize the addition of their effects or achieve their collaborative effect, so as to prevent the increase of cell toxicity and overcome the generation of drug resistance. In the combination of ADM and HD-MTX, each drug can improve the disease-free survival rate by 20%, so it is expected that the disease-free survival rate will be increase by 60%. If HD-MTX and citrovorum factor for rescue is practiced with the combination chemotherapy using ADM, CDP, bleomycin, CTX and ACD, the disease-free survival rate will be up to 76%. Hryniuk *et al.* [4] put forth the concept of dose intensity in the 1980s, which meant that the dose intensity decreased in clinical chemotherapy no matter whether the dose was lowered each time, or the interval between doses was extended. In the animal experiment, lowering the dose intensity of therapeutic drug often significantly reduced the complete response rate and cure rate. Uchida *et al.* [5] applied the HD-MTX, CDP and ADM chemotherapy regimen for two groups of patients with osteosarcoma, who had no obvious difference in gender, age, tumor position, and histological type. When the dose intensity reached or exceeded 80%, the 5-year survival rate was up to 72%. When the dose intensity was <80%, the 5-year disease-free survival rate was only 40%. The lowering of dose intensity was mainly caused by the severe bone marrow suppression, which was most significant in doxorubicin and cisplatin combination chemotherapy. It was followed by the drug (HD-MTX) induced liver disease. Additionally, the postoperative wounds experienced delayed healing or infection, which affected the timely implementation of postoperative chemotherapy.

In the clinical chemotherapy, the dose intensity of chemotherapy has the significantly positive correlation with therapeutic effect and prognosis [5]. To improve the dose intensity of chemotherapy, efforts must be made to prevent the granulocytopenia. At present, the studies focus on supporting the high-dose chemotherapy with granulocyte-colony stimulating factor (G-CSF), autologous bone marrow transplantation (ABMT) and (or) peripheral blood stem cell transplantation (PBSCT), etc. G-CSF can significantly shorten the duration of granulocytopenia, and guarantee the timely implementation of next chemotherapy. In addition, it is convenient to perform clinically, and it has no significant side effects, so G-CSF has now been widely applied in clinic [6].

III. Adjuvant Chemotherapy

Adjuvant chemotherapy normally means to apply the anti-tumor drugs in treating the small lesions that may move to lungs, skeleton, lymph nodes and other positions after surgery is carried out to control local tumor. As proved in tremendous clinical practices, adjuvant chemotherapy is very effective in the treatment of osteosarcoma and Ewing's sarcoma, and can improve the 5-year survival rate significantly.

In the early 1970s, the appearance of adjuvant chemotherapy improved the prognosis of malignant bone tumors significantly. ADM and HD-MTX were effective in the treatment of metastatic osteosarcoma. The therapeutic effect of ADM and MTX general chemotherapy drugs was discovered, which became a major progress in the treatment of osteosarcoma in the early 1970s. The importance of this discovery was reflected not only in the breakthrough for the treatment of late metastatic osteosarcoma, but also in driving the formation of the combination regimens for all kinds of effective chemotherapy drugs in the treatment of osteosarcoma. To improve the survival rate of patients with metastatic osteosarcoma, second-line chemotherapy might be performed besides the active and thorough resection of metastatic lesions. These chemotherapy drugs had higher intensity than the original chemotherapy, so around 50% of the patients could survive for more than 5 years [2]. As revealed in the random testing for 3 groups of patients with lung metastasis of Ewing's sarcoma, the combination of VAC (VCR, ACD and CTX) and ADM could realize the 5-year survival rate of 60%, the combination of VAC and double-lung radiotherapy achieved the 5-year survival rate of 44%, and the single VAC led to the 5-year survival rate of only 24%. Nevertheless,

with regard to Ewing's sarcoma with bone or bone marrow metastasis, Kushner *et al.* [7] recently claimed that the application of chemotherapy and radiotherapy that kill bone marrows could not improve prognosis, so the key was to find new effective chemotherapy drugs. At present, the postoperative adjuvant chemotherapy for malignant bone tumors has been replaced by neo-adjuvant chemotherapy.

IV. Neo-adjuvant Chemotherapy

In the 1970s, another major progress in chemotherapy must be the appearance of preoperative chemotherapy. At that time, it often took more than 3 months to produce artificial prosthesis. Rosen and Marcove in Memorial Sloan-Kettering Tumor Center performed the preoperative chemotherapy for some patients, who were suitable for en bloc resection of tumor and artificial prosthesis replacement surgery, so as to prevent the further development of tumor while waiting for the production of artificial joints. As revealed in the retrospective analysis, the group's survival rate was significantly improved compared with the group receiving the postoperative adjuvant chemotherapy in the same period. In 1979, Rosen *et al.* officially introduced the concept of neo-adjuvant chemotherapy, as the previous chemotherapy was developed for postoperative adjuvant therapy. The neo-adjuvant chemotherapy emphasized that patients should receive preoperative chemotherapy for 6~10 weeks prior to tumor resection, and the postoperative chemotherapy regimen would be developed based on the necrosis of tumor tissues. If the tumor necrosis rate was >90%, the previous chemotherapy regimen would be continued after operation, so the 5-year survival rate could reach 80%~90%. If the necrosis rate was <90%, the 5-year survival rate was lower than 60%, so the postoperative chemotherapy regimen should be adjusted. The concept of neo-adjuvant chemotherapy has now been widely recognized, and become a standard pattern for the treatment of malignant bone tumors [8].

Preoperative chemotherapy was originally developed on the basis of HD-MTX, but single drug could generate the favorable histological reaction among only 15%~20% of patients. By adding CDP/ADM in the chemotherapy regimen and increasing the dose of HD-MTX (from $8g/m^2$ to $12g/m^2$), the reaction rate increased from 18% to 58%. When different combinations of ADM, CDP, IFO and HD-MTX were practiced in other treatment centers, the reaction rate also reached 60%~70%. Wittig *et al.* [1] reported that the application of neo-adjuvant chemotherapy enabled 90%~95% of patients with osteosarcoma to receive the limb salvage treatment, so their 5-year survival rate was up to 60%~80%. The preoperative chemotherapy for Ewing's sarcoma has been taken as a common practice for more than 20 years. Like osteosarcoma, the effect of preoperative chemotherapy could be evaluated through histopathology to identify highly dangerous cases as early as possible. The necrosis rate of tumor cells and disease-free survival rate after chemotherapy relate to prognosis. Preoperative chemotherapy can also realize wider and thorough resection of primary lesions, so as to improve the limb salvage rate. Paulussen *et al.* [3] believed that the combination chemotherapy using ADM, CTX, IFO, ACD, VCR and Vp-16 could help make the 5-year survival rate of patients with Ewing's sarcoma exceed 50%.

Neo-adjuvant chemotherapy has been practiced for years, and become a standard therapeutic regimen for osteosarcoma since the beginning of the 1990s. Neo-adjuvant chemotherapy has the following advantages: (1) it can provide general treatment to eliminate small potential metastatic lesions; (2) it can guide postoperative chemotherapy by evaluating the effect of preoperative chemotherapy; (3) it can reduce the tumor and the reaction zone around the tumor to improve the success rate of limb salvage treatment; (4) it allows sufficient time to design the limb salvage scheme and produce the artificial limb; (5) it reduces the possible spread of tumor during operation; (6) it can identify the group of highly dangerous cases in the early stage.

V. Preoperative Intra-Arterial Chemotherapy

To reduce the systemic toxicity, improve the effectiveness of tumor chemotherapy and enhance the success rate of limb salvage treatment, local arterial chemotherapy may be a feasible method.

Intra-arterial medication can realize higher plateau drug concentration, which exceeds the drug concentration gradient of cells, so as to increase the drug absorption of tumor. The drug concentration inside tumor is directly associated with the level of histological necrosis. When the CDP concentration inside tumor is >16 mg/g, the histological necrosis of tumor is 60%~90%. When the CDP concentration is <12 mg/ g, the histological necrosis of tumor is <40%. Picci *et al.* [9] studied 79 patients receiving arterial and venous CDP chemotherapy. The patients received the general arterial medication of HD-MTX and ADM, and the dose was the same for 3 drugs used in two regimens. As revealed in the results, arterial medication of CDP could make 78% patients achieve the tumor necrosis rate>90%, which was remarkably higher than 46% of patients received venous medication. Hence, arterial medication of CDP has been often advocated in the preoperative chemotherapy of malignant bone tumors today [8, 10]. Local isolation and infiltration chemotherapy, as an intra-arterial chemotherapy, was believed to achieve good local drug concentration and ensure lower systemic toxicity reaction in the past. However, it has been abandoned by famous bone tumor treatment centers in other countries in recent years, as chemotherapy does not mainly aim at small distal metastasis, but at local primary lesions. Local isolation and infiltration chemotherapy could not achieve the effective general plasma concentration, and is often performed once. Moreover, it may cause the swelling and necrosis of soft tissues due to local drug, which affects the limb salvage treatment [6].

VI. Evaluation of Chemotherapeutic Effect for Malignant Bone Tumors

Clinical evaluation is mainly based on whether patients feel the relief of symptoms subjectively, especially reduction of pain and improvement in common conditions, the volume of tumor decreases in clinical examination, tumor has clear boundary with normal tissues, the edematous reaction zone around tumor shrinks, and the activity of peripheral joints is improved, etc. With regard to Ewing's sarcoma, the medical history including increasing erythrocyte sedimentation rate and fever should be also taken as clinical indicators in the observation of therapeutic effect. With regard to imaging diagnosis, the X-ray radiographs before and after chemotherapy are compared, and the indicators for therapeutic effect include increased calcification and ossification of tumor, clear boundary of soft tissue mass, shrinking of mass and clear boundary with normal bone. Enhanced CT and angiography examinations show the decrease or disappearance of tumor angiogenesis, which is an objective indicator in the operation of therapeutic effect. Moreover, the decrease of alkaline phosphatase and succinatedehydrogenase is also one of the indicators for observing the therapeutic effect. The results of isotope bone scanning before and after chemotherapy are compared to find the necrosis of all tumor cells and no live tumor cells. At present, the necrosis rate of tumor is simply divided into good reaction and poor reaction. Based on the results of long-term follow-up visits, Bacci *et al.* [10] pointed out that if the necrosis rate of tissues exceeded 90%, the 5-year survival rate of patients could reach 91%; if the histological necrosis rate of tumor was <90%, the 5-year survival rate was only 38%.

VII. Current Status, Experience and Recommendations of Chemotherapy for Malignant Bone Tumors in China

Since the 1980s, chemotherapy has been carried out for malignant bone tumors represented by osteosarcoma in China. At present, most famous bone tumor centers in China employ the neo-adjuvant chemotherapy, so the limb salvage rate exceeds 70% and the 5-year survival rate is also higher than 50%. However, it is pitiful that there is not a unified chemotherapy regimen in China, and some nonstandard practices of chemotherapy still exist.

We have accumulated the following experience of chemotherapy: (1) when the individual superhigh-dose chemotherapy is practiced, the body surface area is calculated based on the height and weight of patient, ADM 60~80 mg/m^2, CDP100~ 120 mg/m^2, MTX 8~12 g/m^2, and IFO 2 g/m^2. (2) when ADM and CDP arterial cannulation chemotherapy is performed before operation, MTX and IFO are given intravenously, and double-pathway chemotherapy combining artery and vein is

employed, while arterial pump is employed to pump the above drugs and maintain the high plasma concentration. (3) The second-line drug IFO is used in first-line medication to improve the dose intensity of drug. (4) During chemotherapy, it is necessary to carefully observe and record the response of tumor to chemotherapy drug, and learn about which drug the patient is sensitive to, so as to facilitate the preparation of postoperative chemotherapy regimen. (5) If chemotherapy is not very effective, the new drug paclitaxel of175~200 mg/m^2 can be added. (6) In the past, patients had to receive postoperative chemotherapy for 2~3 years. At present, individual superhigh-dose chemotherapy is performed before operation, and achieves good effect, so patients are only required to receive 3~5 courses of postoperative chemotherapy.

Based on the past clinical experience, it is recommended that: (1) the chemotherapy of patients with malignant bone tumors should be carried out at the experienced and advanced chemotherapy center or under the guidance of normally trained professional surgeon for bone tumors; (2) if any patient has good reaction to preoperative chemotherapy regimen, he should better receive the same regimen for postoperative chemotherapy, and any new chemotherapy drug should be used randomly; (3) preoperative chemotherapy should not be limited to 2 courses, and the frequency of chemotherapy should be adjusted based on actual conditions at any time. If there is no reaction or poor reaction to chemotherapy, amputation should be performed in a timely manner to reduce the possibility of metastasis. It is wrong to desire the limb salvage blindly; (4) the metastatic lesions at lungs or other positions may be surgically resected, and good effect can be still achieved by increasing the intensity or using new drug in the postoperative chemotherapy; (5) if any patient faces financial trouble, the chemotherapy relying on ADR and CDP should be selected.

VIII. Development Focuses of Modern Chemotherapy for Malignant Bone Tumors

The survival rate of patients with malignant bone tumors is directly related to the sensitivity of tumor cells to chemotherapy, and depends mainly on the systematic and normalized chemotherapy [10]. Chemotherapy fails some patients because of multidrug resistance. Drug resistance may be primary or secondary. Primary drug resistance refers to the drug resistance that already exists at the time of diagnosis, while secondary drug resistance is caused during the application of chemotherapy. Drug resistance is mainly reflected in: (1) reducing the supply of drug into cells; (2) increasing the metabolism of drug; (2) changing the target enzyme; (4) increasing the recovery of DNA; (5) excessive expression of multidrug resistant oncogene MDR-1 and its gene products. The membrane protein called P-170 relates to drug resistance. Verapamil, immune suppressive agent, hormone, tumor necrosis factor (TNF) and caffeine have the reversion effect of multidrug resistance. All these drugs or compounds can have competitive binding with chemotherapy drugs. As revealed in the results, the concentration degree and range of radioactive nuclide are the important indicators in the observation of chemotherapeutic effect. Among them, isotope 201 thallium (Ti) is observed to have the best effect so far. The most important, sensitive and objective standard for evaluation of preoperative chemotherapeutic effect is the histological reaction of tumor to chemotherapy drug, which also provides the basis for guiding the postoperative chemotherapy. Huvos *et al.* developed the histological classification of tumor reactions to chemotherapy as follows: Class I: there is almost no necrosis of tumor cells; Class II: chemotherapy is slightly effective, the number of tumor cells decreases, the necrosis rate is >60%, and tumor cells still live in some areas; Class III: chemotherapy is effective, the necrosis rate of tumor cells is higher than 90%, and very few live tumor cells still exist. At the drug binding position on the P-170 protein, the efflux of drug from cells decreases, so the concentration of chemotherapy drug inside cells increases to kill tumor cells. In 20 cases of late osteosarcoma, we employed MDR reversal agent and chemotherapy drug for combination therapy, and found that complete response was achieved in 5 cases. In the past, it was believed that the excessive expression of MDR-1 existed in osteosarcoma, rhabdomyosarcoma and Ewing's sarcoma, so the reversion of MDR was crucial to the resolution of multidrug resistance [11]. However, the latest studies claim that the insensitivity to chemotherapy is still affected by many unknown factors due to the heterogeneity of tumor cells, so further research should be carried out [12].

Clinical observation finds that drug resistance to MTX easily happens to tumor cells. At present, the research and development of drug similar to MTX, i.e. Trimetrexate, is under the way. As revealed in the preliminary clinical studies, it was effective in 3 out of 5 recurrent osteosarcoma cases, and complete response was achieved in 1 case. Further experiment is still carried out now, with an aim to make Trimetrexate a substitute drug for patients with drug resistance to MTX. The roles of other new drugs, e.g. immunomodulator, anti-angiogenic factor and growth factor receptor modulator, in the treatment of malignant bone tumors are still further studied.

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