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Review Article

Advances in limb salvage treatment of osteosarcoma

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ABSTRACT

Osteosarcoma is the most common primary malignant bone tumor; its standard treatment includes neoadjuvant chemotherapy combined with surgery. Neoadjuvant chemotherapy has significantly improved the 5-year survival and limb salvage rates in osteosarcoma since the 1870s. The survival rate of patients with limb salvage was not inferior to that of amputees, and therefore, limb salvage has become the main surgical option for patients with osteosarcoma. The 5-year survival rate for osteosarcoma has plateaued. However, new advances in limb salvage therapy in osteosarcoma, including adjuvant chemotherapy, ablation techniques, bone transport techniques, and computer navigation techniques, are now available. This report summarizes the recent advances in limb salvage therapy for osteosarcoma over the past decade.

1. Introduction

Osteosarcoma (OS) is the most common primary malignant bone tumor of the long bones, with children and adolescents at particular risk. OS is a disorder of differentiation in bone arising from mesenchymal tissues. The prevalence ratio among males and females is 1:1.4; the annual incidence rate is 2-3/1000000. This neoplasm also frequently occurs in adults aged 40 and over [1]. The disease is closely linked to several factors, including age, gender, race, height, genetics and congenital abnormalities of bone. Secondary OS is correlated with Paget's disease and radiosensitization [2]. Prior to 1970, the treatment of OS depended primarily on surgical resection, resulting in 5-year survival rates below 20% [3]. Eighty percent of patients diagnosed with have evidence of micrometastasis; the 5-year survival rates in this population are in the range of 10–20%. Since the introduction of effective chemotherapeutic agents in the 1970s and subsequent developments in neo-adjuvant chemotherapy, the prognosis for these patients has improved significantly, with the 5-year survival rates increasing to 66–82% over the past 40 years [4]. Neoadjuvant chemotherapy combined with surgery is now the standard treatment paradigm. With recent advances in surgery, adjuvant chemotherapy, diagnostic imaging, and reconstruction materials, limb salvage has become the main treatment strategy in OS, with approximately 80–85% of patients currently willing to accept this option. This paper reviews the developments in limb salvage treatment for OS in recent years.

2. Development of adjuvant chemotherapy research

The use of drugs including adriamycin (ADM), cisplatin (DDP), high dose methotrexate (HD-MTX), ifosfamide (IFO) and epirubicin (EPI) improves the survival rate of patients with OS [4]. However, high-dose chemotherapy also results in toxicities, including myelosuppression and gastrointestinal reactions. HD-MTX is associated with serious and sometimes fatal toxicity. Chemotherapy dose reduction is an important strategy; therefore, there is a need to ensure the efficacy and simultaneously enhance the sensitivity of chemotherapy drugs. Strategies including the use of aspirin and neoadjuvant chemotherapy with shock waves are new research directions in this area.

2.1. Aspirin-adjuvant chemotherapy in OS

Aspirin is one of the most widely used non-steroidal anti-inflammatory drugs. A randomized controlled trial by Rothwell [5] et al. showed that daily aspirin could reduce the risk of developing colon cancer and metastasis. De et al. [6] observed that different concentrations of aspirin (20/100/1000 μM) could increase the apoptosis rate of osteosarcoma MG-63 cells. They also found that 1000 μM aspirin concentration increased the rate of cell death, while low concentrations of

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1 μM or 10 μM did not. Tang et al. [7] demonstrated that aspirin could inhibit the growth of osteosarcoma and increase the sensitivity to chemotherapy drugs after blocking the NF-κB pathway in vivo and in vitro; other studies confirmed that aspirin could effectively inhibit the NF-κB pathway [8,9]. Liao et al. [10] reported that aspirin controlled the metastasis of osteosarcoma by blocking the NF-κB pathway in cell and animal experiments. This confirmed that aspirin enhanced the therapeutic effect of osteosarcoma in vivo and in vitro. The standard dose of aspirin as adjuvant therapy has not been determined, but in colon cancer clinical research, 75–300 mg is considered low dose and 75–1500 mg is high dose [11]. A recent clinical study of aspirin as an adjuvant treatment in colorectal, breast, stomach, esophagus and prostate cancers at doses of 100 mg and 300 mg daily revealed a dose-dependent effect on tumor prognosis [11]. Liao et al. [10] showed that the aspirin dose for mouse was 100 mg/kg, while it was equal to 8.13 mg/kg for adult. The optimal dosage of aspirin as adjuvant therapy for osteosarcoma could be compared to the dosages for colorectal cancer patients. However, the specific dosage and clinical efficacy require further clarification in future research.

2.2. Extracorporeal shock wave assisted chemotherapy in osteosarcoma

Extracorporeal shock wave therapy has been successfully utilized in patients with kidney stones since reported by Chaussy et al. in 1980 [12]; since then, it has been widely used in the treatment of urinary calculi, with good clinical effect. Further intensive research and development in extracorporeal shock wave has produced promising results in Schleberger and Ludwig's studies of musculoskeletal conditions, such as delayed union, nonunion of long bone fractures and aseptic necrosis of the femoral head [13,14]. Shock waves are the product dramatic changes in pressure; its underlying principle is to form a positive pressure wave by a sharp rise in the medium water vaporizing expansion within a few nanoseconds, and then forming a negative wave by collapsing rapidly and falling sharply and finally causing a cavitation effect under the action of negative wave force [15]. Van Wamel et al. [16] found that the cavitation effect could breakdown the cell membrane associated with jet, microbeam and shock waves, and then form reversible or irreversible holes; this is referred to as "sonoporation". In other words, the cell membrane permeability increased in response to the shock wave, which causes entry of extracellular macromolecular substances into the cell [17]. Kato et al. [18] confirmed that the shock waves promoted bleomycin into human colon cancer cells SW480 in vivo and in vitro by autoradiography. Meanwhile, it improved the curative effect of chemotherapy by increasing cell apoptosis and decreasing the cell proliferation role in solid tumor tissues. Catalano et al. [19] showed that combined with docetaxel, shock waves could be applied in thyroid cancer cell lines ARO and CAL-62. Compared with paclitaxel monotherapy, there were higher concentrations of docetaxel in the tumor cells and a significantly higher cell apoptosis rate in the combined treatment group. Yu and his team members [20] found that low dose shockwaves acton Jurkat cells, and ATP in Jurkat cells was released to outside, therefore, a high concentration of extracellular ATP induced the changes in cell function. Puthussery et al. [21] confirmed apoptosis associated with extracellular ATP concentration. Scholars found that this increased the amount of MTX in U2OS cells and induced its apoptosis after the effect of shock waves in osteosarcoma cell lines in in vitro experiments. At the same time, they also detected a high concentration of ATP outside the cells. Although the related research mainly focused on the cellular level, it is expected to become a new direction for study in the adjuvant treatment of osteosarcoma.

3. Ablation applied in limb salvage surgery in patients with osteosarcoma

Tumor ablation refers to using physical or chemical methods for the in situ elimination of tumor cells. There two methods of ablation: temperature ablation and chemical ablation. Temperature ablation includes microwave, radio frequency (RF), laser, high intensity focused ultrasound ablation and cryoablation. Chemical ablation includes anhydrous alcohol ablation, glacial acetic acid, among others. The treatment of liver cancer is the most common current application of tumor ablation technology. In recent years, ablation has been gradually applied in the limb salvage treatment of osteosarcoma, resulting in favorable clinical curative effect.

3.1. High intensity focused ultrasound ablation

High Intensity Focused Ultrasound (HIFU) is a new non-invasive treatment method for local solid tumors. The operating principle of treatment is that the ultrasound energy is focused in the target tumor tissue; tumor tissue is thus killed by thermal effects and cavitation effects produced by ultrasonic focusing and simultaneously activating the patient's anti-tumor immune system [22,23]. Liet al. [24] found that despite local skin burn and other local complications such as skin dysesthesia when using HIFU to treat 7 patients with limb osteosarcoma, it did have effects on relieving pain and improving local joint activity function. Follow-up results show that the median survival time of the patients is 68 months, and their five-year survival rate is 71.4%. Comprehensive analysis shows that HIFU treatment of an extremity with osteosarcoma is safe and feasible. In addition to the treatment of osteosarcoma, Li and his team members [25] also extended the application of HIFU toother types of primary malignant bone tumors and metastatic bone tumors, and the overall effect on primary malignant bone tumors was 84.6%, while for metastatic bone tumors it was 75%. The 5-year survival rate of primary malignant bone tumors was 38.5%, and for metastatic bone tumors it was 0%. Obviously, the results show that the treatment effect in patients with primary malignant bone tumors is superior to that in patients with metastatic tumors. Chen [26] performed HIFU treatment in 80 patients with primary malignant bone tumors of Enneking stage IIB or phase III to prove that HIFU treatment is feasible and effective, and can be used as a new technology for limb salvage treatment of osteosarcoma in the future. Yu et al. [27] applied HIFU treatment to 27 patients with unresectable locally recurrent osteosarcoma. The statistical results show that the response rate is 51.8%, disease control rates 85.2%, and the median survival time is 21 months. Patients without lung metastasis have better disease control rates and longer time to local disease progression compared to those with lung metastasis. HIFU provides a new direction in the treatment of osteosarcoma limb salvage, but we need to strictly control the indications. At present, the number of treatments is relatively small; large-scale randomized controlled trials still need to be conducted to determine its efficacy.

3.2. Microwave ablation

Microwave ablation is a type of thermal ablation, utilizing 900–2450 MHz radio waves, which can cause intense oscillation of water molecules to create thermogenesis. This method can induce coagulation necrosis of tumor cells [28,29]. The main sequence of microwave treatment of osteosarcoma is: first, separating tumors in vivisection, and at the same time protecting the normal tissue around the tumor after the stripping, to prevent excessive heat damage; second, inactivating the tumor in situ by microwave ablation array with many microwave antennae and eliminating all inactive tissues; finally, using bone cement, allogeneic bone and artificial bone and other biological materials together with strong internal fixation to fill the defect and rebuild mechanical support [30]. Fan et al. [30] used microwave ablation to treat 153 patients with osteosarcoma of extremities; follow-up statistics indicate that the 5-year survival rate was 73.9% and the activity function of the affected limb improved significantly; therefore, microwave ablation is a novel effective treatment for extremities with osteosarcoma. Li and his team members [31] used the navigation