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In Vitro and *In Vivo* Effects of Antiblastic Loaded Polymethyl Methacrylate (Pmma) for the Management of Bone Metastasis: a Literature Review

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Abstract

In the last decades, survivorship of metastatic patients increased so much that orthopaedic surgeons have to perform a long lasting local treatment of bone secondary lesions to improve quality of life.

The treatment has to be personalized for each patient according to tumour prognosis mainly due to histology or solitary/multiple metastases, metastatic localization, patient general conditions, previous normal or pathological ambulation.

In the secondary lower limb lesions, when general conditions and prognosis are good, surgeons have to be aggressive, performing resections and implanting prostheses to allow a quick rehabilitation program. Otherwise, they can perform a more conservative surgery by curettage and local adjuvants in metastatic lower and upper limb lesions, with prognosis and general conditions are poor.

Local treatment of bone metastases with adjuvants has been widely described in literature. The purpose of this review is to consider studies on antiblastic loaded acrylic cement as a treatment option for selected tumors.

Keywords: Metastasis; Bone tumor; Cement; Review

Introduction

The metastatic patient survivorship depends on different prognostic factor as histotypes of tumour and sites of metastases, as Capanna et al. said in 2001 [1]; Capanna developed a predictive scoring table considering different primitive tumour and prognosis (Table 1). He also classified the patients in 4 groups (Table 2) and divided tumours in responsive and non responsive to adjuvant treatment (Table 3). Bone metastasis is a local expression of a systemic disease. Chemotherapy can be used in patient with responsive tumours, according to Karnofsky [2]. Can a local treatment with antiblastic be effective in bone metastases management? Authors tried to explore literature to understand current situation.

Discussion

In 1992 Greco et al. [3] tried to study *in vitro* cytotoxic effect of Polymethylmethacrylate (PMMA) -antiblastic drug compounds in cancer cell lines to explore a new method for local chemotherapy of bone metastasis. They wanted "to analyse the polymerisation capacity of PMMA in the presence of doxorubicin and cisplatinum, the release of drug from the mixture, the kinetics of release, and the effect of the released drugs in normal and neoplastic cell cultures."

On July 2003 Rosa et al. [4] made studies with ultrastructural and in vitro analyses of "Cylinders of manufactured acrylic cement containing three different antiblastic drugs, methotrexate, cisplatin and doxorubicin" to evaluate "the biological effect of the mixtures and surface analysis of the acrylic cement-cisplatin cylinders using energy-dispersive x-ray analysis (EDAX)" on "MCF-7 human breast cancer cells". They prepared cylinders mixing under vacuum "powder (40 g) and a liquid monomer (20ml)" added with "50 mg of cloridrate doxorubicin powder" or "50 mg of cloridrate doxorubicin powder" or "50 mg of cisplatin powder". "After mixing for 100 seconds, the vacuum was removed. The mixture was then poured into the dedicated instrument in accordance with ASTM F-451-959 to make cylinders by compression. The control cylinders were made of cement without drugs using the same process. The cylinders were 10 mm in length and 4 mm in diameter" (Figure 1).

Rosa et al. [4] valued cylinders with EDAX to relieve platinum which is present only in cisplatin mixture and performed a Scanning electron microscopy (SEM) analysis. "The MCF-7 breast cancer cell line was obtained from the American Type Culture Collection and cultured according to the instructions of the supplier in RPMI medium (Gibco) supplemented with 10% heat inactivated foetal bovine serum."

On October 2003, Healey et al. [5] demonstrated that "antineoplastic and antiresorptive drugs added to PMMA cement may prevent local cancer progression and failure of reconstructive devices used to treat patients with pathologic fractures" and they "tested the mechanical properties of cement containing various amounts of the drugs and found that as much as 2 g of either doxorubicin or pamidronate can be

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Survival	Sources of metastasis
Less than one year (1 point)	Unknown
	Melanoma
	Lung
	Pancreas
	Thyroid (undifferentiated)
	Stomach
One to two years (3 points)	Colon
	Breast (not responding to adjuvants)
	Liver
	Uterus (responding to adjuvants)
Over two years (6 points)	Thyroid (differentiated)
	Myeloma
	Lymphoma
	Breast (responding to adjuvants) Rectum

Table 1: Scoring table developed by Capanna.

Class
Solitary Metastatic lesion Primary with good prognosis (well-differentiated thyroid, prostate, breast sensitive to adjuvants, rectum, clear-cell renal, lymphoma, myeloma) Interval over three years since detection of the primary 2. Pathological fracture at any site 3 Impending fracture in a major wright-bearing bone 4 Osteoblast lesions at all sites Osteolytic or mixed lesion in non-structural bones (fibula, rib, sternum, clavicle) Osteolytic lesion with no impending fracture in major weight bearing bone Lesions of the wing of the ilium, anterior pelvis or scapula excluding class-1 patients

Table 2: Group division.

Responsive (0 points)	Breast
	Thyroid
	Myeloma
	Lymphoma
	prostate
Non-responsive (3 points)	Kidney
	Gastrointestinal
	Lung
	Uterus
	Pancreas

Table 3: Responsive or not responsive to adjuvant treatment.

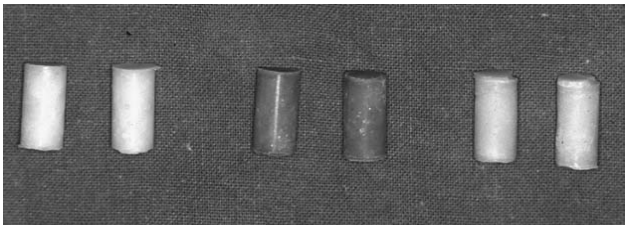

Figure 1: Cemented cylinders.

added to Simplex cement and the cement retains 87% of its compressive and tensile strength after 6 months of wet storage."

In 2005, Cai et al. [6] conducted a study in China to evaluate combination between percutaneous vertebroplasty (PVP) and local antiblastic drugs in vertebral metastases. They selected "Seventy-five patients with vertebral metastases (42 men, 33 women; aged 31-76 years)" who "were divided into 2 groups: 39 were treated by PVP combined with chemotherapy (VPCC group), and 36 were treated by PVP alone (VP group). All procedures were guided by CT scan. The results and complications were evaluated by pain questionnaire and routine follow-up".

In 2007, Maccauro et al. [7] analysed mechanical properties of methotrexate (MTX) added acrylic cement to demonstrate "that the drug is eluted in an active form able to exert a cytotoxic effect over a long period of time. The use of different drug concentrations on the kinetic of elution and on the mechanical properties of cement was also evaluated".

In 2013 Özben et al. [8] shown that the addition of cisplatin doesn't interfere with the mechanical properties of PMMA, and could exert cytotoxic action on osteosarcoma cell culture.

In 2014 Liao et al. [9] affirmed "the addition of MTX to CPC does not significantly affect the basic crystal structure and setting time of Calcium Phosphate cement (CPC).

In a more recent study Kiri et al. [10], first tried the addition of MTX to aluminum-free glass ionomer cements (GICs). These materials, commonly used in dental applications, set via a neutralization reaction between a basic glass powder and an aqueous solution of polyalkenoic acid, usually poly- acrylic acid (PAA). When mixed, the acid attacks the glass, liberating metal cations, which then crosslink the polyanion groups of the acid, producing a polysalt matrix reinforced by reacted and unreacted glass particles [11]. The results showed that MTX was readily released by the GIC without compromise to the therapeutic potential of the drug or the handling and mechanical utility of the material.

In Greco's paper [3] results showed that "even at high concentrations neither doxorubicin nor cisplatinum inhibit the polymerization of PMMA. Moreover, mixtures in vitro can release the antiblastic drug which maintains its pharmacologic activity on sensitive neoplastic cells. Therefore, the PMMA-antiblastic drug mixtures, along with current anti-cancer therapy (systemic chemotherapy and radiation therapy), may provide better local control of the metastatic lesion and of some bone tumors."

Rosa et al. [4] demonstrated that "all drugs were released in an active form from the cement. Each drug had a different effect on cell viability. Doxorubicin had the greatest effect on breast cancer cells. Surface analysis showed that antiblastic drugs were present in the form of granules".

Healey et al. [5] said that "one half of the drug elution occurs within the first day in experiments that combined doxorubicin and pamidronate, and within 3 days when pamidronate was the only additive."

Cai et al. [6] affirmed that "Response rate was significantly higher in percutaneous vertebroplasty combined with chemotherapy group than in vertebroplasty group (93.0% vs. 74.4%, $P < 0.05$); complete response rates of VPCC group and VP group were 25.6% and 10.3%. Common complication of VPCC was transient aggravation of pain".

Maccauro et al. [7] explained that "the release of MTX is higher at the beginning and progressively decreases over time being affected by the concentration of drug used".

The use of doxorubicin added to cement is indicated in breast cancer metastases, cisplatin in lung cancer metastases and methotrexate

in other tumours. Doxorubicin lasts for only 24 hours and is toxic for heart, while methotrexate is aspecific and toxic for kidneys [12], so some patients cannot tolerate the drug use although folic acid rescue properties have to be considered [13].

Selected patients have to be in good clinical conditions according to Karnofsky [2].

The chemotherapy has a central role in responder tumour type [1,2], while radiotherapy may anyway help in local control after curettage and cement [12].

Rosa et al. [4] affirmed that "when antiblastic drugs are included in cement they remain metabolically active. The duration and extent of their effect were found to vary according to the type of drugs but were potentially clinically relevant and not affected by the time interval between manufacture and implantation of the cement."

Healey et al. [5] concluded that cement containing antiblastic and antiresorptive drugs "seems to be strong enough, but its fatigue strength should be tested before using it clinically. Sufficient amounts of the tested drugs elute to have potential biologic activity."

Cai et al. [6] demonstrated "PVP may release the pain and consolidate the vertebrae of patients with vertebral metastases. Its short-term effect may be enhanced by adding drugs into bone cement."

According to Maccauro [7] "elution of MTX does not alter the compressive properties of the cement" and its use can be "an effective aid for the management of bone metastases requiring surgical curettage and acrylic cement implantation for structural support". Also Handal et al. [14] confirmed with their analysis method that "the addition of methotrexate to PMMA in concentrations of 1.8 g methotrexate per 40 g PMMA did not change the compression modulus of the cement pre- or post-elution of drug".

Kiri et al. affirmed [10]. "The most significant finding of this study was that MTX was readily released from the glass ionomer cements (GIC), while maintaining cytotoxic activity. Release correlated linearly with initial loading and appeared to be diffusion mediated, delivering a total of 1-2% of the incorporated drug. MTX loading in this range exerted minimal effects to handling and strength, indicating the clinical utility of the material was not compromised by MTX loading.

In conclusion we can summarise that in some metastatic histological pattern, local control of the disease can be better obtained with tumour specific antiblastic loaded Polymethylmethacrylate. Metastatic desease may also benefits from radiotherapy and chemotherapy when feasible.

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