Journal of Bone Oncology 26 (2021) 100345

Contents lists available at ScienceDirect

Journal of Bone Oncology

journal homepage: www.elsevier.com/locate/jbo

Review Article

Bone cement as a local chemotherapeutic drug delivery carrier in orthopedic oncology: A review

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ARTICLE INFO

Article history:
Received 6 November 2020
Revised 8 December 2020
Accepted 11 December 2020
Available online xxxx

Keywords:
Metastatic bone cancer
Orthopedic surgery
Bone cement
Antineoplastic drugs
Local chemotherapy

ABSTRACT

Metastatic bone lesions are common among patients with advanced cancers. While chemotherapy and radiotherapy may be prescribed immediately after diagnosis, the majority of severe metastatic bone lesions are treated by reconstructive surgery, which, in some cases, is followed by postoperative radiotherapy or chemotherapy. However, despite recent advancements in orthopedic surgery, patients undergoing reconstruction still have the risk of developing severe complications such as tumor recurrence and reconstruction failure. This has led to the introduction and evaluation of poly (methyl methacrylate) and inorganic bone cements as local carriers for chemotherapeutic drugs (usually, antineoplastic drugs (ANPDs)). The present work is a critical review of the literature on the potential use of these cements in orthopedic oncology. While several studies have demonstrated the benefits of providing high local drug concentrations while minimizing systemic side effects, only six studies have been conducted to assess the local toxic effect of these drug-loaded cements and they all reported negative effects on healthy bone structure. These findings do not close the door on chemotherapeutic bone cements; rather, they should assist in materials selection when designing future materials for the treatment of metastatic bone disease.

Contents

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https://doi.org/10.1016/j.jbo.2020.100345
2212-1374/

1. Introduction

Cancer cells are prone to metastasize to the skeleton and cause secondary bone lesions. The incidence of metastasis and subsequent survival is heavily dependent on the location of the primary tumor [1,2]: 65–75% in the breast (19–25 months survival); 65–75% prostate (12–53 months); 60% in thyroid (48 months); 30–40% in the lung (6–7 months) and 40% in bladder (6–9 months) [1]. Furthermore, according to the World Cancer Research Fund International, lung, breast, colorectal and prostate cancer are the four most common cancers worldwide [3] suggesting that the majority of patients suffering from cancers are at high risk of developing bone metastasis. Patients diagnosed with bone metastasis are at risk of developing severe pain, life-threatening hypercalcemia due to elevated blood calcium levels and weak bones leading to pathological fracture [4].

Mirels' classification is a scoring system used by surgeons to assess metastatic bone lesions and predict the likelihood of an impending pathological fracture [5,6]. Mirels' classification grades secondary cancers based on four variables (Table 1), where each variable is assigned a score (1–3). The sum of these scores (4–12) is used to determine the treatment for the affected area, with higher numbers correlating to a higher likelihood of developing a pathological fracture. Bone with a Mirels' score $\leq$8 may be prescribed bone modifying agents, such a bisphosphonate or a monoclonal antibody that binds to receptor activation of nuclear factor-kappa ß ligand [6,7]. In contrast, bones with a Mirels' score $\geq$9 are recommended to undergo prophylactic fixation [6] which involves the excision of the cancerous tissue and reconstruction of the damaged bone [8].

The options for bone fixation vary depending on the patient's age, life expectancy, functional demands, and method of tumor excision [9,10]. The majority of patients diagnosed with metastatic bone cancer are expected to have a limited life expectancy. Therefore, the goal of this treatment is palliative in nature; it reduces pain and restores function to the affected bone for the duration of the patient's life [11]. Thus, synthetic implants, which are composed of metallic (usually, titanium alloys and stainless steel) [12,13] polymeric (usually, ultra-high molecular weight polyethene) [12] and ceramic (usually, zirconia or alumina) [14] materials are chosen for metastatic bone reconstruction due to their ability to allow for early weight-bearing and mobility [11,15–17]. The type of synthetic replacement chosen (osteosynthetic implant or prosthetic replacement) depends primarily on the location and extent of bone destruction [18].

Osteosynthetic implants include an array of plates, intramedullary (IM) nails and orthopedic screws [12,13]. They are often preferred as they restore the function of the affected limb while preserving the native joint and is a less aggressive/invasive procedure compared to endoprosthetic reconstruction [19,20]. Prosthetic implants are generally chosen for more severe bone lesions (where the lesion exceeds 50% diameter of the bone or when it affects a joint) [21,22]. Protheses are superior to osteosynthetic devices as they exhibit greater torsional strength and immediate stability/mobility [23,24]. However, prosthetic implants also experience higher rates of complications compared to osteosynthetic devices [19]. Reasons for implant failure include infection (0–11.7%), aseptic loosening (0–12.5%), and mechanical failure (0–14.7%); furthermore, although chemotherapy is generally administered post-reconstruction, tumor recurrence continues to present itself as a prevalent issue (3.1–14.7%) [25–31].

To minimize post-surgical complications, many surgeons use cemented reconstruction techniques, whereby poly (methylmethacrylate) (PMMA) bone cement is implemented as an adjunct for bone reconstruction. The use of bone cements as a chemotherapeutic drug carrier in an attempt to reduce tumor recurrence has been the subject of many studies in the literature. The purpose of this review was to critically examine this body of work.

2. PMMA bone cement

Introduced and patented as Perspex® in the 1930s, PMMA was originally used to make airplane windows and canopies during World War II [32]. During the 1940s, the composition was modified for dental applications and in 1958, PMMA bone cement was introduced as an adjunct for orthopedic implants [33,34].

PMMA bone cement is comprised of powder and liquid-based components: the powder components are pre-polymerized PMMA beads, an initiator (benzoyl peroxide) and a radiopaque element (BaSO4 or ZrO_2 particles). The liquid components are the monomer, methylmethacrylate (MMA), an activator (N, dimethyl-para-toluidine), and a small amount of hydroquinone to ensure that polymerization does not take place during storage [35,36]. The relative amounts of these constituents vary between different cement brands. Additionally, some cement brands are loaded with antibiotic(s) for the purposes of combatting periprosthetic joint infection [37]. Before implantation, the powder and liquid components are mixed under a vacuum to reduce porosity and enhance the mechanical properties of the cement [38].

2.1. PMMA bone cement as an adjunct

PMMA bone cement is injected into the space between the implant and the surrounding bone. The cement's initial fluidity facilitates it filling both the pores of the cancellous bone and any additional voids. Virtually immediate fixation is achieved upon cement curing (a setting time of ~15 min) due to the high degree of mechanical interlocking between both the bone and cement

Table 1
Summary of Mirels' scoring system for predicting the likelihood of an impending fracture [6].

Score	Site of Lesion	Size of Lesion	Nature of Lesion	Pain
1	Upper Limb	<1/3 of the cortex	Osteoblastic	Mild
2	Lower Limb	1/3–2/3 of cortex	Mixed	Moderate
3	Trochanteric region	>2/3 of the cortex	Osteolytic	Functional

and the cement and implant [39]. Furthermore, the cement also acts as a buffer to reduce stress shielding; a physical phenomenon whereby bone atrophy results from a significant reduction in the load experienced by the bone adjacent to an implant [40]. This phenomenon may lead to aseptic loosening [40,41]. Metallic materials have a significantly higher modulus (E = 110–210 GPa) [40,42] compared to trabecular bone (E = 4.7–15.5 GPa depending on the anatomical location) [43] and, as a result, cause a high degree of stress shielding. In contrast, the modulus of bone cement (2.6 GPa) [44] is closer to that of trabecular bone and, as a result, is thought to work as a buffer between the two materials. However, Zhang and colleagues [45,46] have postulated that stress shielding may still occur at the bone-cement interface, suggesting a loss in the interlocking of the bone-cement interface over time. Nevertheless, cemented fixation has been shown in clinical case series to offer greater rigidity and implant fixation in the metastatic bone cancer population compared to traditional non-cemented methods (press-fitting/locking). For instance, Benevenia *et al.* reported a 21% versus 33% complication rate when comparing cemented and non-cemented endoprostheses, respectively [47]; similarly, Wedin *et al.* reported an 11% versus 19% failure rate when comparing cemented and non-cemented osteosynthetic devices, respectively [19]. Moreover, Habermann *et al.* noted that six non-cemented fixation failures could have been prevented with the use of bone cement [48].

Patients undergoing cemented reconstruction may also experience greater levels of pain relief and functional restoration [48]. Laitien *et al.* reported that the use of opioids and other narcotics were considerably lower when patients underwent cemented reconstruction [49]. In fact, the analgesic effect of PMMA bone cement is so significant that procedures which solely utilize the bone cement are considered as palliative treatment options for patients suffering from secondary bone cancer (*i.e.,* cementoplasty).

2.2. PMMA bone cement-exclusive techniques

Cementoplasty is a minimally invasive and radiologically-guided technique in which PMMA bone cement is percutaneously injected into the osteolytic region of a damaged bone and is an acute treatment for patients who are ineligible for complete surgical reconstruction due to poor oncologic/clinical status [50,51]. This technique was initially implemented as a reconstructive surgery for cases of spinal metastasis, known as vertebroplasty (VP) [52,53]. PMMA bone cement was found to be especially advantageous in this scenario, as its compressive strength is high enough (~93.0 MPa) [44] to support the forces experienced by the spinal column [53,54]. Furthermore, researchers also discovered that a high percentage of VP patients experienced moderate to complete pain relief post-surgery [55]. These realizations ultimately extended the procedure's use to cases of extraspinal malignancies (cementoplasty).

Although PMMA has a high compressive strength, it is susceptible to failure under torsion [56,57]. Therefore, percutaneous long-bone cementoplasty (PLBC) is reserved as a palliative treatment to reduce pain, provide some degree of mechanical support, and improve the quality of life of patients who are unable to undergo complete reconstruction [56–58]. A study conducted by Cazzato and colleagues [56] suggested that PLBC is most effective when the largest dimension of the metastatic lesion is <3 cm, and that upper limb treatments encounter greater levels of pain relief. Moreover, several studies have highlighted that cementoplasty does not provide adequate mechanical support for lesions of the lower limbs [56,59,60]. Deschamps *et al.* [60] reported a 33% fracture rate in 21 patents (mean Merils' score of 9.8) who underwent PLBC for metastatic lesions of the proximal femur. Fractures took place a mean of 48 days after the procedure [60]. A review of the literature found that 78% of patients experienced functional improvement and 96% of patients experienced moderate to complete pain relief following PLBC [58].

It has been suggested that the analgesic effect of PMMA bone cement can be attributed to two phenomena: 1) penetration of cement into the trabecular bone, stabilizing existing macro- and microfractures and, hence, reducing micromotion in the affected area [50,51] and 2) during implantation, the setting PMMA undergoes polymerization; the exothermic reaction heating the surrounding bone up to 70 °C [61,62] which can cause tissue necrosis of the nociceptive nerve terminals, thus numbing pain [56,57,63,64]. However, studies by Kallmes *et al.* [65] and Buchbinder *et al.* [66] suggest that the analgesic effect might be nothing more than a placebo effect. In both investigations, patients with painful osteoporotic vertebral fractures were randomly placed in one of two groups: one group underwent VP, while the other underwent a sham procedure (in which all steps, including the preparation of PMMA bone cement, were performed with the exception of the actual insertion and injection of the cement). In either case, the authors reported no significant difference between the groups with regards to pain relief [65,66]. No such trials have been performed for patients with cancerous lesions. Furthermore, while it may be argued that the application of the heat from the bone cement elicits a local antitumoral effect by causing thermal necrosis of cancer cells [64] this cytotoxic effect is limited to only 3 mm around the cement and therefore, is insufficient to operate as a valid antitumor therapy [57].

2.3. PMMA bone cement-chemotherapeutic drug carrier

Despite resection of the tumor and consequent chemotherapy, tumor recurrence continues to present itself as a prevalent issue. The progressive growth of the tumor and ensuing osteolysis may result in loosening and failure of the supporting implant [26,67]. A group of chemotherapeutic drugs known as antineoplastic drugs (ANPDs) are generally administered post-surgery (orally, intermuscular, intravenously or intrathecally) in an attempt to mitigate this issue [68]. However, these systemic modes of administration often achieve only low local (target) drug concentrations due to tissue ischemia, resulting in a minimized local effect [69,70]. Furthermore, ANPDs are among the most toxic medically administered compounds [71]. The therapeutic index of a drug is an indicator of its relative safety and is calculated as the ratio of its effective concentration to its minimum toxic concentration. For many ANPDs, the therapeutic ratio is ~1 [68,71]. For instance, methotrexate (MTX) is an ANPD that is used to treat a wide range of cancers (including primary and secondary bone cancers). It acts by inhibiting the synthesis of DNA, RNA, and proteins of rapidly proliferating cells [68]. However, MTX has a broad range of general toxic effects, including agranulocytosis, anemia, thrombocytopenia, neutropenia, hyperbilirubinemia, nausea, vomiting, and diarrhea [68]. In an attempt to achieve high local drug concentrations and improve the therapeutic index of an ANPD, researchers have employed PMMA as a drug carrier in order to prevent local tumor growth and implant failure as well as to reduce systemic concentrations and the degree of systemic side effects [72]. This idea was inspired by the introduction, in the 1970s, of antibiotic-loaded PMMA bone cement as a means of delivering high local concentrations of antibiotics to the periprosthetic tissue [73,74].

2.3.1. ANPD incorporation, drug elution studies and mechanical effects

Several ANPDs have been tested in conjunction with PMMA bone cement, including MTX, cisplatin, doxorubicin, 5-fluorouracil, and zoledronic acid [67,69,70,72,75–88]. The incorporation of the chosen ANPD generally occurs by blending the drug with the powder component of the cement, prior to the addition of the liquid

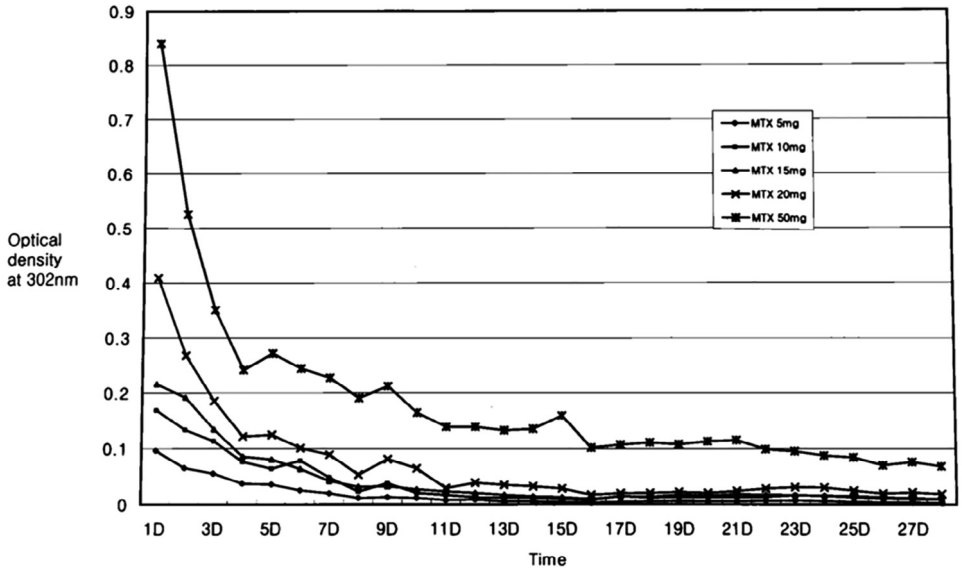

Fig. 1. Results from the drug elution study performed by Kim et al. [85] demonstrate the poor elution properties of PMMA bone cement. Specimens were prepared by mixing 40 g of cement powder with 20 mL of cement liquid and either 5, 10, 15, 20 or 50 mg of MTX powder. Cement pellets (12 mm diameter by 2 mm height) were placed in 5 mL of HBSS (Hanks' balanced salt solution), where the HBSS was collected and replaced every 24 hours for four weeks. MTX elution was qualified daily *via* spectrophotometry. The mean MTX released over the experiment was 9.6% (7.2–11.7%) of the total amount incorporated, with most of the release occurring within the first 24 h.

[76,77,79,80]. In a few cases, the drug was incorporated by first blending it with the liquid component [80,81,83]. Prochazaka *et al.* [80] compared the incorporation of MTX in either the powder or the liquid, finding that the powder-incorporated specimens demonstrated greater drug elution profiles. However, similar to antibiotic-loaded PMMA bone cements, the elution of ANPDs from PMMA bone cement is suboptimal [84].

In many studies, it has been reported that only 5–20% of the incorporated ANPD elutes from the cement when exposed to an aqueous environment [85,86,89]. Furthermore, the majority (up to 10%) of this release occurs within the first 24 hours(Fig. 1) [76,83,85,86]. In one instance, Wasserlauf *et al.* [78] found that MTX-, cisplatin-, and 5-fluorouracil-loaded cements only released 6%, 3.4%, and 3.3% (respectively) of their total incorporated amount when exposed to a physiological solution for six months *in vitro*. It is speculated that these low drug elution rates are a result of the non-biodegradable nature of the cement [67,72,77,79]. Scanning electron microscopy (SEM) revealed that ANPD-loaded PMMA bone cements have granules of drug powder on their surfaces as opposed to the beaded surfaces found from non-drug loaded cements [67,72,77,79]. Furthermore, Özben *et al.* [72] performed SEM imaging of cisplatin-loaded cement before and after 15 days of elution in cell media (Dulbecco's Modified Eagle's Medium), discovering that the number of granules/mm^2 on the surface had decreased over time, further suggesting that it is only the drug particles on the surface that elute while the drug incorporated into the cement bulk remains trapped.

Handal *et al.* [84] demonstrated that it is possible to increase elution (up to 60% of the incorporated amount) of MTX-loaded bone cement with the addition of a soluble filler (polyethylene glycol, PEG), which dissolves to increase the pores within the bulk of the cement, thus allowing for increased drug elution. However, the authors [84] did not report the mechanical properties of the PEG-MTX-incorporated bone cements. Only a limited amount of MTX may be loaded because high amounts have deleterious effect on mechanical properties of the cement [67].

According to Wang *et al.* [67] the investigations of antibiotic-loaded bone cement lead to the general acceptance that up to 2 g of antibiotics can be added per 40 g of cement powder (CP) to avoid adverse effects on the cement's mechanical properties. Wang *et al.* formulated several PMMA bone cements, loaded with different amounts of MTX (0 g, 0.1 g, 0.5 g, 1 g and 2 g/40 g CP), and subjected them to compression, shear and 4-point bending tests. No significant differences were found between the compressive strengths nor between the elastic moduli. However, the shear strength and the 4-point bending failure load decreased for the cements loaded with amounts > 1 g MTX/40 g CP [67] suggesting a limitation on the amount of ANPD that can be incorporated.

2.3.2. In vitro studies

In many short-term *in vitro* tests, it was shown that loading the cement with a small amount (<1 g/40 g CP) of ANPD was sufficient to kill cancer cells [70,72,77,79,90]. Furthermore, these tests demonstrated that the pharmaceutical properties of ANPDs remain stable after experiencing the high temperatures reached during PMMA's exothermic polymerization reaction. For instance, Rosa *et al.* [77] performed an *in vitro* test on three different ANPD-loaded cements: an MTX-loaded cement (0.1 g/40 g CP), a doxorubicin-loaded cement (0.05 g/40 g CP), and a cisplatin-incorporated cement (0.05 g/40 g CP). Cylindrical samples (diameter and length of 4 mm and 10 mm, respectively) were prepared from each cement and incubated in 4 mL of RPMI cell media for 15 days, where media was changed every 24 h and stored at −80° C [77]. The media at each time point was then added to a 24-well plate, seeded with MCF-7 breast cancer cells, and after 48 h of incubation, the cell viability of each well was tested *via* an MTT assay [77]. As displayed in Fig. 2, all of the drug-loaded cements had a significant effect on cell survival at 24 h; 51.6% for MTX, 68.2% for cisplatin and 10.4% for doxorubicin. However, cell survival increased for each cement with increasing time points, and with the 15-day media, cell survival was 90.5% for MTX, 98.8% for cisplatin, and 98.6% for doxorubicin [77]. From this body of data, Rosa *et al.* concluded that MTX had a more stable release and cytotoxic activity compared to the other ANPDs. However, in this study, twice as much MTX was incorporated as was done with the other two drugs, and the authors made this assumption based off the cell survival data, with no supporting evidence from elution studies [77].

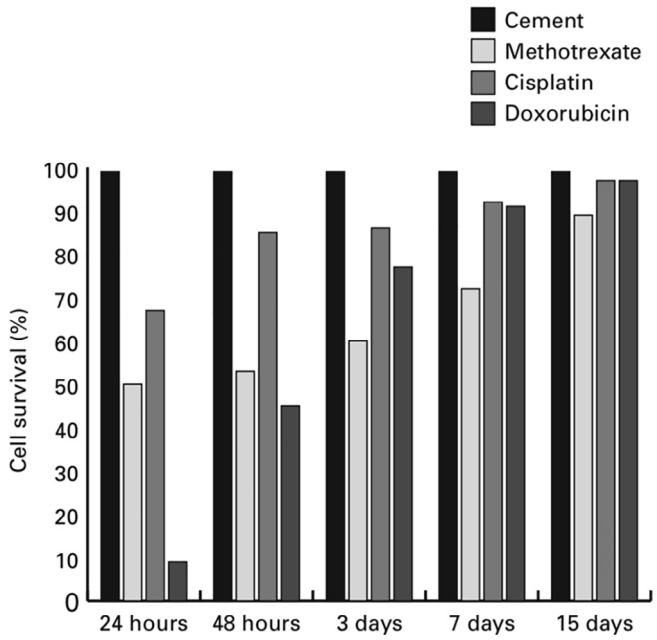

Fig. 2. Results from the *in vitro* test conducted by Rosa et al. [77] normalized by the control's MTT results (Cement). MCF-7 Breast Cancer Cell survival is shown for media collected from the three ANPD-loaded cements at 24 h, 48 h, three days, seven days, and 15 days.

Greco *et al.* [70] compared the effect of high loadings of cisplatin and doxorubicin on both colon (WIDR) and breast cancer (CG-5) cell lines, reporting similar cell survival stability for both drugs, as Rosa *et al.* [77] concluded for MTX. The cumulative data from these studies suggest that the stability of a long-term cytotoxic effect on cancer cells is dependent on the initial concentration of the ANPD loaded into the cement, a finding that is consistent with the trends in drug elution rates found by Kim *et al.* [85]. As seen in Fig. 1, the higher the initial concentration of the incorporated ANPD, the greater the release at each respective time point. However, results from *in vivo* trials suggest that other factors may play a role in the stability of local drug release and the cytotoxic effect.

2.3.3. In vivo trials

Four *in vivo* trials have been conducted on ANPD-loaded bone cements in order to assess the ability of the drug carrier to maintain high local concentrations and minimize systemic concentrations [75,76,87,88]. Llombart-Blanco *et al.* [87] performed VP on 20 landrace female pigs, injecting half with MTX-loaded bone cement (1 g/22.5 g CP) and the other half with cisplatin loaded bone cement (0.5 g/22.5 g CP). Bone biopsies were performed weekly to assess the local concentration of the drug and blood samples collected periodically within the first 72 h post-implantation. Contradictory to the results of the *in vitro* experiments conducted by Rosa *et al.* [77] Llombart-Blanco *et al.* [87] demonstrated that even at half the concentration, cisplatin displayed a more stable local drug concentration compared to MTX over the 5-week trial (Table 2).

Cisplatin bone tissue concentrations remained relatively high for the first three weeks of implantation (mean = 1148 mg/mg bone) and continued to fluctuate until the end of the experiment. In contrast, MTX bone tissue concentrations followed a more expected pattern dictated by the drug elution profiles discussed earlier [87]. Curiously, the systemic concentrations of cisplatin remained relatively consistent throughout the first 72 h of implantation (mean = 0.195 μmol/L), while MTX systemic concentrations decreased drastically within the first 48 h [87]. In either case, the authors reported no signs of systemic toxicity. The results obtained by Llombart-Blanco *et al.* [87] indicate that the ability of an ANPD-loaded cement to maintain stable drug concentrations depends on the ability of the drug to diffuse from the bone tissue into systemic circulation. Systemic concentrations should be monitored long-term to gain insight into the relationship between local and systemic drug concentrations. Furthermore, the incorporation of each ANDP should be studied extensively. A review of the literature reveals that MTX-loaded PMMA cements have been the subject of many more studies than cements loaded with any other ANDP [67,69,70,72,75–88].

2.3.4. Local toxicity of MTX-loaded PMMA bone cement

Hernigou *et al.* [76] performed the seminal study on ANPD-loaded bone cement in 1989 and tested the cement in three independent *in vivo* trials. Their first trial was performed on 100 rats induced with experimental osteosarcoma using the protocol designed by Allouche et al. [91] whereby radioactive cerium hydroxide was injected into the hind leg, in close contact to the bones of the knee joint. Rats were then randomized into groups: 20 rats received no treatment, 20 rats received an implant without MTX (placed at the center of the tumor), and 60 rats received an MTX-loaded implant (placed at the center of the tumor) [76]. Results demonstrated that MTX-loaded implants were successful in destroying the tumor (75–90% necrosis) and that the overall toxicity depended on the dosage of the drug [76]. For instance, the 10 rats implanted with the highest dose (5 mg MTX) suffered a high mortality rate (90%) between the fourth and sixth days of implantation, while rats implanted with 1.5 mg of MTX had their survival period extended by an average of 30 days [76]. These results revealed that high doses of local therapy have the ability to induce high systemic drug concentrations and toxicities.

Next, the authors performed a trial on 17 dogs (30–80 kg) with spontaneous osteosarcoma [76]. Tumors were excised without any safety margin of bone and the defect was fixed with an osteosynthetic device and then filled with MTX-loaded bone cement (total of 100 mg MTX in 14 cases, 200 mg in two cases and 500 mg in one case) [76]. By the end of the experiment (8 months), only 10 dogs (58.8%) survived; 3 (17.6%) experienced tumor relapse, 2 of which were euthanized at the request of their owners and the third had an amputation. The experiment was deemed a success as the osteosarcoma experienced by the dogs had previously been shown to lead to a local rapid relapse with standard management.

Table 2
Results from *in vivo* experiments conducted by Llombart-Blanco *et al.* [87].

Mean Systemic (Blood Plasma) Drug Concentrations (μmol/L)			Mean Local (Bone Tissue) Drug Concentrations (μg/mg bone)		
Time	Cisplatin	MTX	Time	Cisplatin	MTX
30 min	0.198	0.922	Week 1	1160.3	862.76
8 h	0.2	0.492	Week 2	920.2	605.98
24 h	0.222	0.044	Week 3	1394.6	169.93
48 h	0.202	0.024	Week 4	482.1	214.85
72 h	0.151	0.023	Week 5	600.5	7.53

Unfortunately, this experiment was performed without a control group (0 mg MTX). Furthermore, 3 animals (2 weighing <50 kg) that were injected with 200 mg MTX experienced systemic side effects, two of which were cured while the third died, further suggesting that the weight of the patient should be considered when deciding ANPD dosage. Moreover, 4 of the animals (23.5%) experienced delayed wound healing within the first 15 days of implantation, two of which required removal of the cement [76]. Finally, Hernigou *et al.* reported a small sample of data from a clinical trial, where 14 patients (with either primary or metastatic cancer) were treated by tumor resection and the bone defect repaired with a metal implant fixated with MTX-loaded bone cement (100 mg total MTX) [76]. The authors confirmed high local and low systemic drug concentrations; however, two (14.3%) of the patients experienced wound healing complications, with one patient requiring cement removal [76]. Overall, the results from these preliminary experiments suggest that high local concentrations of MTX may cause undesirable local toxic effects, which may jeopardize long-term implant fixation.

Three studies have highlighted the local toxic effects of MTX-loaded bone cements [80,81,83]. Draenert *et al.* [81] used eight German giant rabbits to assess the bone-compromising side effects of MTX-loaded bone cement. The rabbits were operated on both knees, where implantation sites were drilled for the press-fit insertion of cement cylinders (diameter and length = 4.6 mm and 6 mm, respectively). Six rabbits received an MTX-loaded cylinder (either 200 mg, 1 g or 4 g MTX/40 g CP) in one knee and a control cement (0 mg MTX) in the other knee, while the remaining two rabbits received control implants in both knees [81]. All animals tolerated the MTX-loaded cement with no complications, and after 35 days of implantation, the rabbits were euthanized and samples harvested [81]. In-depth histological studies revealed growth inhibition and thinner trabeculae, 2 mm around the MTX-loaded cement samples [81] suggesting that MTX-loaded bone cement may encounter issues with bone healing and may compromise implant fixation.

Furthermore, two *in vitro* trials highlighted the cytotoxic effects of MTX on healthy bone cells. Decker *et al.* [83] assessed the cytotoxicity of MTX-loaded cement on five osteosarcoma cell lines as well as on an osteoblast cell line. Cylinders (diameter and height = 24 mm and 10 mm height, respectively) were fabricated out of an MTX-cement (250 mg MTX/40 g CP) and placed in sterile vials filled with 20 mL of RPMI-1640 cell media, where media was removed, stored and replaced every 24 h. The osteosarcoma cell lines were cultured using 1-day (high concentration), 2-day (medium concentration), and 10-day (low concentration) eluates while the osteoblast cell line was only cultured with the 10-day eluate [83]. Cell viability was studied *via* an MTT assay, where (regardless of the low concentration), 10-day eluates caused a 20% decrease in osteoblast cell survival [83]. Moreover, Prochazaka *et al.* [80] demonstrated the side effects of MTX on mesenchymal stem cells (MSCs), which are multipotent cells that differentiate into bone cells and are primarily located within the bone marrow. MSCs were sourced from the bone marrow of healthy donors and were cultured with MTX-loaded cement cylinders (0 mg, 40 mg or 400 mg MTX/40 g CP) for 14 days where the analysis of cell viability and proliferation was performed after one, three, seven, ten and 14 days [80]. Results demonstrated that MTX did not have a significant effect on cell viability; however, it was found to stunt mitosis, as the authors reported an accumulation of stem cells in the S and G2 phases of the cell cycle. This impairment of the ability of MSCs to divide further stresses the local toxicity of MTX-loaded bone cement and its potential to compromise the cellular integrity of bone and the fixation of the supporting implant, resulting in aseptic loosening, an issue present with current non-drug loaded PMMA cement.

2.4. Cytotoxic effects of PMMA bone cement

Aseptic loosening is one of the most common causes of endoprosthetic failure. In addition to the phenomenon of stress shielding discussed in Section 2.1, research has proposed that these failures may be linked to specific cytotoxic effects elicited by PMMA bone cement, which contribute to aseptic loosening by destroying bone cells and increasing osteoclast activity [92–96]. The following section will discuss these cytotoxic effects.

As reported in Section 2.2, exothermic temperature reached during the polymerization of PMMA bone cement is high enough to cause an antitumoral effect [64]; however, it also causes thermal necrosis of healthy bone cells, which can die at temperatures as low as 45 °C [97]. A study conducted by Wang and colleagues [98] highlights the drastic differences between healthy and necrotic bone, where micro-CT imaging relieved that the trabecular structure of necrotic bone is damaged, suggesting a decrease in mechanical interlocking with PMMA. Furthermore, an array of histological tests and stains suggested that necrotic bone tissue had increased osteoclastic activity, further indicating that the gradual resorption of the bone-cement interface may ultimately cause aseptic loosening [98]. ISO Standard 5833 states that the maximum exothermic temperature of an acrylic bone cement must be <90 °C [99]; however, research has shown that lower temperatures ($\approx$ 50°C) can still cause thermal necrosis [100–103].

It has been widely reported that thermal necrosis of bone is a function of the temperature to which the bone is exposed (T_B) and the exposure time (t_E) and bone necrosis has a delayed effect (*i.e.,* it occurs when 30 s < t_E < 400 s) when $T_B \approx 50$ °C, as opposed to when $T_B > 60^o$ C, where bone necrosis may occur instantaneously (*i.e.,* $t_E > 0$ s) [100–102]. Fukushima *et al.* [103] demonstrated (during cemented total knee arthroplasty) that, with a cement layer 2 mm thick, the maximum temperature at the bone-cement interface was 53 °C, 200 s after the start of the polymerization of the cement, with bone necrosis being observed at a depth of 1 mm from the bone-cement interface. Furthermore, the study demonstrated that by thinning the cement layer to 1 mm, both the maximum temperature experienced the reaction (46 °C), and the overall depth of necrosis (<1 mm) could be reduced, suggesting that the total volume of cement may affect values of T_B. Several studies have noted similar trends [101,103,104]. This positive correlation should be highlighted for cases of bone cancer reconstruction, as higher levels of bone destruction may require larger volumes of PMMA bone cement to achieve sufficient implant fixation, which may result in a higher degree of overall thermal necrotic damage and increased risk of aseptic loosening.

In addition to thermal necrosis, PMMA bone cement also exhibits a toxic chemical effect known as monomer toxicity, which is caused by the release of residual, unreacted MMA monomer from the polymerized cement [39,105–107]. MMA is lipolytic and, therefore, can cross the plasma membrane and has specifically been shown to induce apoptosis in both osteoblasts [108] and osteoblast-like cell-lines *in vitro* [109]. Furthermore, the cement can also prompt an immune response, known as periprosthetic osteolysis, whereby particulate debris released from the cement throughout *in vivo* service triggers the activation of macrophages and the release of several cytokines and cell mediators that promote osteoclast activity [93,94,106,110]. The combination of these effects may ultimately increase subsidence at the bone-cement interface, resulting in aseptic loosening.

Researchers have attempted to alter the composition of PMMA bone cement to reduce these cytotoxic effects, although the literature reveals that most of these studies failed to produce any significant improvements [33,111]. Furthermore, as discussed in Section 2.3, the addition of chemicals often has detrimental side effects on other properties of the cement, including strength and

biocompatibility [33,111,112]. Thus, the array of unavoidable compromises residing in PMMA bone cement have inspired researchers to investigate new cements for orthopedic applications.

3. Inorganic bone cements

Advancements in biomaterials and understanding the bioactive mechanisms of hard tissues (*i.e.,* bone and dentine) have led to the development of inorganic cements such as calcium phosphate, calcium sulphate, calcium silicate, zinc phosphate, zinc polycarboxylate, and glass polyalkenoate cement [113]. While their inferior mechanical properties have confined the majority of their use to dental, craniofacial, and maxillofacial applications [113,114] their biocompatible and osteoconductive characteristics have sparked interest in extending their use to orthopedic applications [115,116]. Furthermore, their biological properties may oppose the toxic nature of ANPD-incorporation and support osteogenesis. Specifically, calcium phosphate and glass polyalkenoate cements have been evaluated pre-clinically as local chemotherapeutic drug carriers.

3.1. Calcium phosphate cements

Calcium phosphate cements (CPCs) were first commercialized for clinical use in 1996 for the purposes of treating maxillofacial and minor fracture defects [113,117]. Since then, several compositions have been proposed for various applications such as cranioplasty [117] VP [118] and the fixation of metallic implants [119,120]. For instance, Nakamura et al. [120] utilized CPC for the treatment of benign bone tumors in 33 pediatric patients and in three cases the cement was used as an adjunct to osteosynthetic devices [120].

The powder of a CPC is composed of one or more calcium orthophosphates (*i.e.*, tetracalcium phosphate, α-tricalcium phosphate, *etc.*) and the liquid is either water or an aqueous solution (usually, 0.05% phosphoric acid) [121,122]. When mixed, the calcium orthophosphate(s) undergo an isometric dissolution and precipitation process, whereby the entanglement of precipitated crystals is responsible for cement hardening [121,122]. Based on the composition, the end product of CPC can be tailored to resemble biological hydroxyapatite [113,115,121,122]; therefore, CPCs are bioactive (that is, display osteointegration and bioresorbability) [113]. Furthermore, their porous structure makes them excellent candidates as local drug carriers.

3.1.1. CPC-chemotherapeutic drug carrier: ANPD incorporation, drug elution studies, and mechanical effects

Several ANPDs, including 6-mercaptopurine (6-MP), cisplatin, doxorubicin and MTX, have been tested in conjunction with CPCs [123–129]. Similar to drug-loaded PMMA bone cements, CPCs incorporated with ANPDs exhibit a biphasic release pattern when exposed to an aqueous solution [125,127,128]. However, the overall efficiency of drug release from CPCs (14–64% of the incorporated drug) [125,127,128] is markedly higher than that from PMMA bone cements (5–20%) [85,86,89].

Otsuka and colleagues were the first to investigate ANPD-loaded CPCs [123,124]. In their preliminary study [123] the researchers loaded a CPC with 6-MP in both a homogeneous and heterogeneous manner. Homogeneous specimens were prepared by adding 25 mg (5 wt%) of 6-MP to the pre-mixed CPC paste. Cylindrical specimen (15 mm diameter) were formed and mounted in beeswax such that one surface of the CPC was exposed to the environment. Heterogeneous specimens were prepared by compressing 6-MP powder into solid pellets (25 mg), which were then placed on nondrug-loaded CPC cylinders and fixed with beeswax such that only the surface of the CPC was exposed to the environment [123]. Drug release was tested using the rotating disc method (150 rpm) in 25 mL of simulated body fluid (SBF), where the SBF was collected and replaced at suitable intervals over 570 h, and 6-MP elution was quantified *via* spectrophotometry [123]. Cumulative release from the homogeneous and heterogeneous specimens were 68% and 28%, respectively. Furthermore, the heterogeneous system had a lag time of 70 hoursbefore drug elution was initiated, suggesting that the micropore structure of the cement changed over time and allowed 6-MP to elute from under the cement bulk [123]. Moreover, in their later study, Otsuka *et al.* [124] demonstrated that both CPC pore volume and drug elution could be elevated by increasing the liquid-to-powder ratio (LPR). However, the authors did not determine the mechanical properties of the cement [123,124].

Increasing the LPR has been shown to significantly decrease mechanical properties of CPCs [130,131]. Furthermore, similar to PMMA bone cement, there is a limit to the amount of ANPD that can be loaded into a CPC without causing detrimental effects on the cement's mechanical properties. For instance, Yang *et al.* incorporated 0, 80, 200 and 400 mg (0-1 wt%) of MTX into 40 g of CPC powder prior to mixing with 16 mL of solution [128]. Cylindrical specimens (diameter and length = 8 mm and 12 mm, respectively) were prepared and tested to calculate the compressive strength (CS) and tensile strength (TS) of the four cements [128]. Results demonstrated that both the CS and TS decreased with increasing MTX loading. Moreover, significant differences were observed between the 0 mg cement (CS = 40.06 MPa, TS = 12.25 MPa) and the 400 mg cement (CS = 37.6 MPa, TS = 9.92 MPa) [128]. As discussed in Section 2.3.1, Wang *et al.* [67] demonstrated that PMMA bone cements experienced a significant decrease in mechanical properties when 1 g MTX was added to 40 g CP (2.5 wt%). The results from these two studies suggest that the mechanical properties of CPCs are more sensitive to incorporation of ANPDs compared to the cases when PMMA bone cement is used.

3.1.2. CPC-chemotherapeutic drug carrier: In vitro and in vivo studies

Two studies have been performed to assess the anti-cancer effects of ANPD-loaded CPCs [126,127]. Tani *et al.* [126] performed an *in vitro* and *in vivo* test on a CPC loaded with doxorubicin (10 g CP, 3.6 mL solution and 10 mg (0.1 wt%) doxorubicin). The *in vitro* trial demonstrated that the CPCs eluted doxorubicin (collected daily over 14 days), successfully restrained cell proliferation of RMT-1 E4 rat mammary carcinoma cells [126]. Furthermore, during their *in vivo* trial, 32 ICR mice were induced with a tumor (sarcoma 180 cells) on their backs [126]. After an unspecified growth period, 1 mL of CPC gel, loaded with (n = 16) or without (n = 16) doxorubicin, was injected into the center of the tumor. Subsequent growth was monitored weekly by measuring the major axis of the tumor for 16 weeks. Results showed that the doxorubicin-loaded CPCs successfully suppressed tumor growth throughout the entire experiment (significant differences observed during the first four weeks). Furthermore, the survival rate of the mice in the doxorubicin-loaded CPC group (75%) was higher than that of those in the CPC-only group (12.5%) [126].

Tanzawa *et al.* [127] demonstrated that the local antitumor effects of cisplatin-loaded CPCs could be greatly enhanced with the additional incorporation of caffeine. Four sets of cements were formed by mixing (Group A) CPC alone (20 g CP), (Group B) CPC + caffeine (1 g), (Group C) CPC + cisplatin (100 mg) and (Group D) CPC + caffeine + cisplatin. During their *in vitro* trial, cement cylinders (diameter and length of 7 mm and 14 mm, respectively) were prepared and placed in 10 mL of media for seven days, where the media was changed every 24 h and stored at −80 °C [127]. SOSN2 (rat osteosarcoma) cells were seeded in 100-cc plates and preincubated for 24 h. From then on, the media was replaced with the

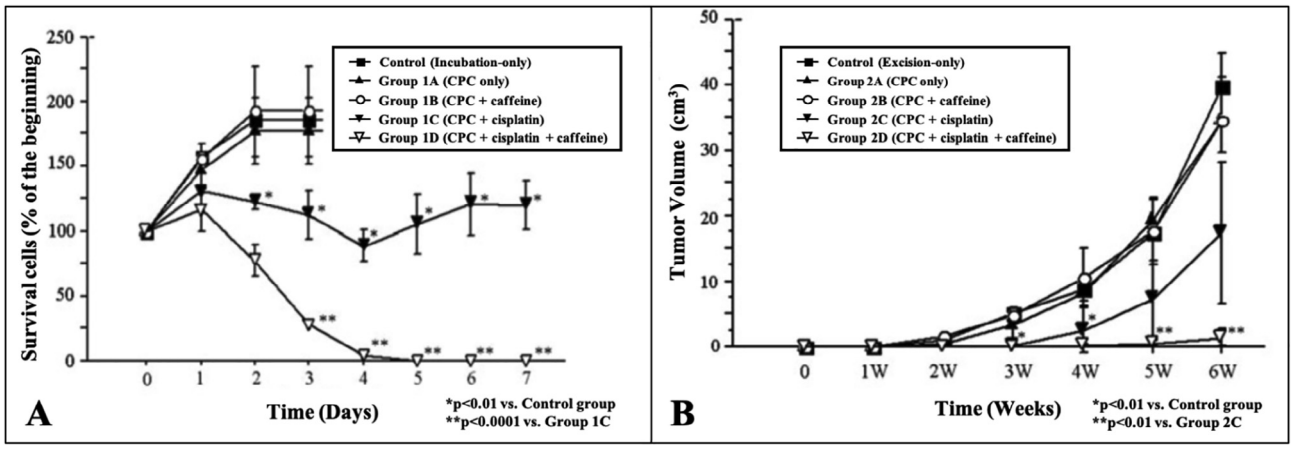

Fig. 3. Results from the *in vitro* test (A) and *in vivo* test (B) performed by Tanzawa et al. (Adapted from [127]).

1-day media for the first period (0-24 h), the 2-day media for the next period (24–48 h), and so on for 7-days. Cell survival was determined by counting the cells every 24 h. The results (Fig. 3A) demonstrate that Group C was successful at suppressing cell growth compared to the control, Group A and Group B; however, Group D outperformed all the other groups, killing the cells by the fifth day [127]. Moreover, during their *in vivo* study, holes (2 mm-by-4 mm) were drilled into the tibias of 7-week-old, Fischer 344/NSlc rats. Matrigel® (Becton-Dickinson Co., Bedford, MA) was then mixed and injected with a suspension of SOSN2 cells to create a gelatinous tumor, which was then placed inside the medullary space and left there for 3-days to allow the cells to enter the surrounding tissue [127]. The rats were then split into five groups: control (excision only), and those whose medullary space was filled by injecting one of the four CPCs (Groups A-to-D). Tumor growth was monitored weekly for six weeks by calculating its volume [127]. The results (Fig. 3B) support the findings of their first experiment, that group D was the most successful in suppressing tumor growth. A study by Yasutake *et al.* [132] demonstrated that caffeine works synergistically with cisplatin by inhibiting repair of the DNA damaged by the cisplatin. However, caffeine alone has also demonstrated unfavorable side-effects on healthy bone cells [133] and may also enhance local cytotoxicity of ANPDs.

3.1.3. CPC-chemotherapeutic drug Carrier: Local toxicity

Two studies have suggested that the local toxicity of ANPDs may still interfere with healthy bone when CPC-loaded bone cement is used [125,129]. Tahara *et al.* [125] performed histological examination of Japanese white rabbits implanted with cisplatin-loaded CPC (various amounts of incorporation; 0 mg (0 wt%), 7.5 mg (5%), 15 mg (10%), and 30 mg (20%)). Rabbits had 5 mm-diameter holes drilled into their distal femurs, and cement cylinders (diameter and length of 4 mm and 5 mm, respectively) were implanted into the medullary space. Rabbits implanted with the 0% and 5% implants were exposed 2, 4 and 6 weeks after implantation (two rabbits per implant per time point; 12 rabbits total). Rabbits implanted with the 10% and 20% implants were exposed at 2, 4, 6 and 12 weeks (16 rabbits total). Rabbit femurs were harvested at the time of euthanasia, and bone formation was examined under a light microscope [125]. Results demonstrated that the formation of new bone was increasingly delayed with increase in cisplatin concentration. Bone formation was observed at: week 2 for 0% implants, week 6 for 5% implants, week 12 for the 10% implants, and no bone formation was observed by week 12 for the 20% implants. While their study may have incorporated higher amounts of cisplatin (0–20%) [125] Tahara *et al.* demonstrated the negative effects of ANPD-loaded CPCs on osteogenesis.

Li and colleagues [129] investigated the effects of CPCs loaded with 1 wt% of MTX on osteogenesis and CPC degradation. Twenty-four New Zealand rabbits had holes (diameter = 3 mm) drilled into the lateral side of the left femoral condyle. The defect was then filled with a pre-set CPC loaded with (n = 12) or without (n = 12) MTX [129]. Three rabbits from each group were euthanized 1 day and, 1, 3 and 6 months post-implantation and the left femurs were harvested. Sections of the femurs were stained with hematoxylin and eosin and observed under a light microscope to determine the extent of osteogenesis [129]. A significant difference between the two groups was observed at 3 months, where the plain (non-loaded) CPC appeared to have undergone significant degradation, while the MTX-loaded CPC appeared unchanged from the 1 day samples [129]. However, at 6 months, both cements seemed identical in terms of degradation.

Moreover, the presence of osteoblasts (osteoblast index (OBI)) and osteoclasts (osteoclast index (OCI)) were determined *via* alkaline phosphatase (ALPase) immunohistochemistry and tartrate-resistant acid phosphatase (TRAPase) enzyme histochemistry (respectively). New bone volume (NBV) was also determined and expressed as a percentage of newly formed bone at each of the mentioned time points [129]. Each of the aforementioned parameters remained lower for the MTX-loaded CPC compared to CPC alone, showing significant differences at 1 month. Furthermore, the OCI remained significantly lower for the MTX-loaded CPC 3 months but, by 6 months, matched the level for CPC alone [129]. Overall, this study demonstrated that 1 wt% incorporation of MTX is enough to delay osteogenesis and CPC degradation by at least three months.

In a previous study, Yang et al. [128] showed that the 1% MTX-CPC released ~64% of the incorporated amount over 30 days *in vitro*. Therefore, it could be estimated that most of the incorporated MTX must have eluted from the cement after 3 months, but, before 6 months, its toxic effect on healthy cells stopped, allowing osteogenesis to continue. However, the interaction of CPCs and lytic metastatic cancer sites should be studied thoroughly.

3.1.4. CPC-Chemotherapeutic drug carrier: contradictions

Aside from their poor mechanical properties, biodegradability of CPCs may turn out to be a severe drawback to their use in orthopedic oncology. As the majority of metastatic cancer sites are lytic (bone-resorbing) in nature [134] the introduction of bulk, resorbable calcium phosphate may initiate or aggravate hypercalcemia.

Therefore, the use of CPCs may pose a contradiction when used to reconstruct of bones damaged by metastatic bone cancer.

3.2. Glass polyalkenoate cements

Glass polyalkenoate cements (GPCs) have been used in dentistry for over 40 years and in ear, nose and throat surgery for over 20 years [135–137]; however, the presence of aluminum (Al) in the glass phase of commercial GPCs have inhibited their extension to orthopedic applications [138,139]. Recent advancements in glass science have facilitated the development of Al-free GPCs [140–148]. The powder component of a GPC is an ionomeric silicate-based glass, while the liquid component is aqueous polyacrylic acid (PAA). When mixed, the components undergo an isothermic neutralization reaction, whereby the protons, from the aqueous PAA, attack the glass phase and liberate cations, which then cross-link the polymer chains of the PAA. The resultant is a polysalt matrix reinforced by reacted and unreacted glass particles [145,149,150].

The rheological and mechanical properties of a GPC are strongly influenced by 1) LPR, 2) the molecular weight of the PAA, and (3) the composition of the glass phase [146–148]. Furthermore, the glass phase can be loaded with various ions that are released by GPC, which can promote osteogenesis and elicit antibacterial properties [151,152]. To the best of the present authors' knowledge, there has only been one study that investigated the potential for using GPC as a chemotherapeutic drug carrier [153].

3.2.1. GPC–chemotherapeutic drug carrier

Kiri *et al.* [153] performed experiments on a GPC loaded with various amounts (0 wt%, 1%, 5% and 10%) of MTX. The incorporation of MTX demonstrated no adverse effects on the compressive strength of the GPC, exhibiting statistically significant increases for the 1% and 5% samples [153] and suggesting that the mechanical properties of GPCs are less sensitive to ANPD incorporation compared to the case with either PMMA bone cement or CPCs [67,128]. Drug elution was assessed by placing cement cylinders (diameter and height = 4 mm and 6 mm, respectively) in 10 mL of phosphate-buffered saline (PBS), which was then incubated at 37 ^{O}C in a 2-Hz rotating mixer, where the PBS was collected, stored and replaced at suitable intervals over 31 days and MTX elution was quantified *via* UV/Vis spectroscopy [153]. Cumulative MTX release over the duration of the experiment was low: 1.7%, 1.4% and 1.7% for the GPC loaded with 1%, 5% and 10% of MTX, respectively, with most of the release occurring within the first 24 h [153]. It was suggested that this low release rate could be explained by the presence of two carboxylic groups on MTX that may have interacted with the eluted cations, which chemically bonded them to the PAA chains [153–155]. This bonding could also potentially explain the increase in strength caused by MTX incorporation; however, more research is required to understand the effects of MTX incorporation on the polysalt matrix of a GPC.

Kiri *et al.* also performed an *in vitro* cytotoxicity test by culturing NIH-3 T3 mouse fibroblast cells with the extracts collected from 1, 7, and 31 days. The results from the MTT assay revealed that the MTX-loaded GPCs were toxic to the cells, suggesting that ANPD toxicity may continue to present itself as an issue [153].

4. Conclusions

Metastatic bone lesions are common among patients with advanced cancers [1,2]. The predominant treatment for severe metastatic bone lesions is reconstruction surgery [8]. Various synthetic materials have been used for bone reconstruction; however, many of these materials exhibit complications. PMMA bone cement has been implemented as an adjunct for reconstruction materials and reduces the rate of failures and complications [19,47] but has not completely eliminated the occurrence of either infection or aseptic loosening; furthermore, despite resection of the tumor and consequent chemotherapy, tumor recurrence is a prevalent issue driving reoperation [25–31]. Hence, innovation is required not only to reduce the rate of complications but also to improve the efficiency of chemotherapy.

Inspired by the incorporation of antibiotic(s) into bone cement, researchers have formulated ANDP-loaded PMMA bone cement in an attempt to reduce the rate of tumor recurrence and improve the therapeutic index of these toxic drugs [72]. In many studies, achievement of providing high local concentrations while minimizing systemic concentrations has been demonstrated [75,76,87,88]. However, few have considered the local effects of ANPDs on healthy bone cells [80,81,83] discovering evidence of local toxicity.

PMMA bone cement has its share of cytotoxic effects, including thermal necrosis, monomer toxicity, and periprosthetic osteolysis. While providing some degree of antitumor activity by killing local cancer cells [64] the innate cytotoxicity of PMMA bone cement may cause implant failure due to its effects on healthy bone cells [98,108,110]. Attempts to modify the composition of PMMA bone cement have resulted in unavoidable compromises between these cytotoxic effects [33,111]. Alternatively, researchers have investigated the use of inorganic bone cements (CPCs and GPCs) as local chemotherapeutic drug carriers. CPCs have been demonstrated to act as efficient drug carriers [125–128]; however, their resorbable properties may initiate or aggravate cases of hypercalcemia when introduced to a lytic bone environment [134]. GPCs have very low drug elution rates; however, their mechanical properties appear to be less sensitive to ANPD incorporation than is the case with PMMA bone cement and CPCs, allowing for larger amounts of drug incorporation [153]. Despite their osteoconductive properties, it has been suggested that the local toxicity of ANPD-loaded inorganic bone cements on healthy bone tissue may present complications with osteogenesis [125,129,153].

Results of the literature studies reviewed in this work do not close the door on chemotherapeutic bone cements for orthopaedic oncology; rather, they should assist in materials selection when designing future materials for the treatment of metastatic bone disease. An ideal bone cement for the reconstruction of metastatic bone lesions should possess the following properties in order to ensure long-term fixation:

1) Elicit a chemotherapeutic effect, with an acceptable therapeutic index
2) Elicit an antibacterial effect, with an acceptable therapeutic index
3) Set at body temperature
4) Possess osteoconductive properties in order to accelerate and maintain osteointegration
5) Possess mechanical properties similar to those of trabecular bone in order to prevent stress shielding.

Funding

This work was supported by the Natural Sciences and Engineering Research Council (NSERC) (Discovery grant # RGPIN-2019-04634), the Canadian Institutes of Health Research (project grant # 399463) and the Ireland-Canada University Foundation (the James M. Flaherty Visiting Professorship scheme), all awarded to Dr. Towler.

CRediT authorship contribution statement

Sunjeev S. Phull: Investigation, Writing - original draft. **Alireza Rahimnejad Yazdi:** Conceptualization, Writing - review & editing. **Michelle Ghert:** Validation, Writing - review & editing. **Mark R. Towler:** Supervision, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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