REVIEW ARTICLE OPEN

The strategy and clinical relevance of in vitro models of MAP resistance in osteosarcoma: a systematic review

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Over the last 40 years osteosarcoma (OS) survival has stagnated with patients commonly resistant to neoadjuvant MAP chemotherapy involving high dose methotrexate, adriamycin (doxorubicin) and platinum (cisplatin). Due to the rarity of OS, the generation of relevant cell models as tools for drug discovery is paramount to tackling this issue. Four literature databases were systematically searched using pre-determined search terms to identify MAP resistant OS cell lines and patients. Drug exposure strategies used to develop cell models of resistance and the impact of these on the differential expression of resistance associated genes, proteins and non-coding RNAs are reported. A comparison to clinical studies in relation to chemotherapy response, relapse and metastasis was then made. The search retrieved 1891 papers of which 52 were relevant. Commonly, cell lines were derived from Caucasian patients with epithelial or fibroblastic subtypes. The strategy for model development varied with most opting for continuous over pulsed chemotherapy exposure. A diverse resistance level was observed between models (2.2–338 fold) with 63% of models exceeding clinically reported resistance levels which may affect the expression of chemoresistance factors. In vitro p-glycoprotein overexpression is a key resistance mechanism; however, from the available literature to date this does not translate to innate resistance in patients. The selection of models with a lower fold resistance may better reflect the clinical situation. A comparison of standardised strategies in models and variants should be performed to determine their impact on resistance markers. Clinical studies are required to determine the impact of resistance markers identified in vitro in poor responders to MAP treatment, specifically with respect to innate and acquired resistance. A shift from seeking disputed and undruggable mechanisms to clinically relevant resistance mechanisms may identify key resistance markers that can be targeted for patient benefit after a 40-year wait.

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INTRODUCTION

Osteosarcoma (OS) is the most common malignant bone cancer and affects approximately 2.5 per million people in England equivalent to 135 cases per year [1]. OS is more common in males [1–3] and a higher incidence rate has been observed in Black patients [2, 3]. The peak age at diagnosis of bone sarcoma for females and males is 13 and 15–17 years, respectively [2]. This reflects a pattern of disease progression in line with growth, with bone development occurring approximately 2 years earlier in pubescent females than males [4]. A second peak is also evident in those above 65 years and is associated with Paget's disease [1, 3, 5], secondary cancer [3] and a poorer outcome [5].

The 5-year survival rate increased from 17% [6] to 68% [7] for OS patients with localised disease during the 1970s when chemotherapy was introduced into practice. However, whilst the average 5-year survival for all cancer patients increased by around 20% from 1980 to 2010 [8], 5-year overall survival and recurrence rates for localised OS have stagnated since the 1980s [9]. This is despite an increase in the rate of limb-salvage surgery owing to advancement in surgical technique and earlier detection [9]. This lack of progress is impacted by an absence of improved treatment options over the last 40 years with approximately one third of patients relapsing commonly more than once [10, 11], with overall survival for these patients reported at 23–29% [10, 12]. In addition, 16% of patients have detectable metastases at diagnosis and up to 77% of these will succumb to the disease within 5 years [13].

Although the introduction of chemotherapy drastically changed the extremely low survival rates achieved with surgery alone, OS is regarded as relatively chemoresistant as many single agents have shown poor responses in patients. The drugs methotrexate (at a high dose, hdMTX), doxorubicin (DOX), cisplatin (CDDP) and ifosfamide (IFOS), collectively known as MAPi, have the highest single agent response rates ranging from 30 to 40% [14]. Current therapy therefore involves a combination of these agents, with patients receiving two 5-week neoadjuvant cycles followed by a further 4–6 adjuvant cycles as part of the widely adopted EURAMOS-1 protocol [15]. Multiagent chemotherapy is used to circumvent a single resistance mechanism as each agent has a unique target. Specifically, the alkylating agent CDDP enters cells via passive diffusion [16] and creates inter- and intra-strand DNA adducts that induce apoptosis [17]. The alkylating agent IFOS which is a derivative of nitrogen mustard also induces DNA damage similarly through cross-linking [18]. The anthracycline DOX isolated from Streptomyces peucetius var. caesius [19] enters

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