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Review Article

Adjuvant bisphosphonate treatment for breast cancer: Where are we heading and can the pre-clinical literature help us get there?

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ABSTRACT

Bisphosphonates have demonstrated anti-tumour activity in preclinical studies of bone metastatic disease, thus it was natural to transition these agents into the adjuvant cancer therapy setting. Surprisingly, the results of adjuvant breast cancer trials have shown either modest to no benefit or even harm. We sought to explore whether the preclinical results supporting bisphosphonate use provided clues to help explain the current clinical data. Interestingly, the majority of preclinical data suggested that bisphosphonate treatment was more efficacious when administered after the establishment of osseous metastases. This is similar to the findings of one clinical study whereby patients with biopsy evidence of osseous micrometastases derive greater survival benefit from bisphosphonate treatment. Another clinical study found bisphosphonates were associated with increased incidence of visceral metastases, similar to what has been previously published in preclinical models using "preventative" dosing strategies. While the current clinical data suggest bisphosphonates may be more efficacious in post-menopausal or oestrogen depleted patients, or those with hormone receptor positive tumours, to date no appropriately designed preclinical studies have evaluated these effects. Furthermore, putative mechanisms that regulate response to bisphosphonates in other tumour types remain to be evaluated in breast cancer. Despite the initial optimism regarding adjuvant bisphosphonate therapy, the conflicting clinical results from large trials suggest that we should return to the bench to further investigate factors that may influence response to bisphosphonate treatment or identify appropriate characteristics that would indicate the sub-groups of patients most likely to benefit from bisphosphonate treatment.

1. Background

Following the publication of a number of preclinical studies suggesting that bisphosphonate treatment could significantly impair the growth of osseous breast tumours, and stabilise bone metastases, a number of clinical studies were initiated to evaluate the effects of adjuvant bisphosphonate treatment in newly diagnosed breast cancer patients. Now that many of these studies have reached clinical maturity, their published results have been either positive [1–4] negative [5–8], or even detrimental [9], (see Table 1). Although certain factors have been suggested to influence the clinical responses noted with bisphosphonate use (Fig. 1), formal demonstration of their association has yet to be determined. Given these conflicting clinical outcomes and the extensive preclinical data that was supposed to support the adjuvant development of these agents, it is time to revisit the published preclinical results in order to determine whether they predicted the current clinical outcomes.

2. Preclinical studies: Of mice, rats and women?

2.1. Preclinical animal models and dosing regimens

To date, a number of factors that may influence tumour response to bisphosphonates have been suggested by preclinical studies (Fig. 2). The studies referenced by the published clinical trials cite data restricted to 4 different preclinical models of osteolytic bone metastases, one human, one mouse and two rat-derived tumour cell lines. While in all cases inhibitory effects on skeletal metastases were observed (summarised in [10]), the

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Table 1

Characteristic	Diel et al. [2], Annals of Oncology, 19:2007		Powles et al. [1], Breast Cancer Research, 8:R13		Gnant et al. [3,4], The Lancet, 12:631		Coleman et al. [5], New Eng J of Med, 365:1396		Kristensen et al. [6], Acta Oncologica, 47:740		Saarto et al. [9], Acta Oncologica, 43:650	
Bisphosphonate used	Clodronate	Placebo	Clodronate	Placebo	Zoledronic acid	Placebo	Zoledronic acid	Placebo				
Pamidronate	Placebo	Clodronate	Placebo									
Dosing schedule and route	1600 mg orally daily for 2 years	No	1600 mg orally daily for 2 years	Yes	4 mg IV every 6 month for 3 years	No	4 mg IV every 3–4 weeks for 6 cycles then every 3–6 months for 5 years	No	150 mg orally twice daily for 4 yrs	No	1,600 mg orally daily for 3 yrs	No
Use of anti-estrogens	47% received tamoxifen	45% received tamoxifen	80% of cohort received tamoxifen		100% of cohort received either Tamoxifen or		anastrozole		78.3% on endocrine or endocrin-e+			
chemotherapy	78.6% on endocrine or endocrine+						chemotherapy	Endocrine therapy excluded	Endocrine therapy excluded	100% of cohort received tamoxifen or toremifene		
Cohort size	157	145	530	539	900	903	1681	1678	460	493	139	143
Mean age	NR 52	NR	52.8	52.7	44.5	44.5	NR	NR	[b]	[b]		
T-stage												
T1	38%	37%	26%	26%	75.7%	76.7%	32.2%	31.2%	41%	44%	51%	46%
T2	45%	46%	57%	57%	21.2%	21.7%	50.6%	51.7%	50%	50%	42%	46%
T3 or greater	17%	16%	9%	10%			17.0%	17.1%	7%	5%	7%	6%
Unknown			8%	7%	2.1%	2.6%	0.2%	0.1%	2%	1%	0	3
Lymph node positive	51%	54%	37%	38%	30.5%	30.5%	97.8%	97.7%	75%	75%	99%	99%
Menopausal status												
Pre-menopausal	36%	39%	50%	49%	NR	NR	44.7%	44.8%	67%	66%	48%	57%
Post-menopausal	64%	61%	50%	51%	NR	NR			33%	34%	52%	43%
Post-menopausal < 5yrs							14.7%	14.5%				
Post-menopausal > 5yrs							30.9%	31.1%				
Unknown							9.8%	9.5%	0%	0.2%		
ER status												
Positive	75%	71%	46%	45%	94.6%	93.3%	78.5%	78.4%	13.5%	17.2%	61%	68%
Negative	25%[a]	29%[a]	26%	25%	3.3%	3.9%	20.8%	21.1%	60.4%	52.9%	35%	23%
Unknown			28%	30%	2.1%	2.6%	0.8%	0.4%	26.1%	29.8%	4%	9%
PR status												
Positive	62%	63%	21%	22%	89.9%	89.5%	NR	NR	11%	11%	50%	60%
Negative	38%[a]	67%[a]	15%	14%	7.6%	8.3%	NR	NR	29%	28%	45%	31%
Unknown			64%	65%	2.5%	2.2%	NR	NR	60%	61%	5%	9%
Pretreatment evidence of bone metastasis	Yes	Yes	No	No	No	No	No	No	No	No	No	No
	Positive – Increased OS at 8.5 years post-treatment. – No difference in DFS or incidence of metastases at 8.5 years post-treatment.		**Positive** – Decreased incidence of bone metastases at 5 years post-treatment. – Trend for better OS at 5 years post-treatment.		**Positive** – Reduced incidence of DFS events at 5 years post-treatment. – No difference in OS.		**Negative** – No differences in OS, DFS at 5 years post-treatment.		**Negative** – no differences in OS, DFS or incidence of metastases at 5 years post-treatment		**Negative** – no significant differences in OS or frequency of metastases at 10 years post-treatment – decreased DFS and increased extraskeletal metastases in clodronate group at 10 years post-treatment	

NR—Not Reported.

[a] Not originally reported therefore may contain negative and unknown categories.

[b] Mean age for treatment groups was not reported however was stratified across 4 groups originally; for pamidronate and control cohorts there were 61.3% and 63.1% of patients younger than age 50 respectively.

models differed in their results with respect to their effects on extraskeletal metastases. The studies using preclinical models of human breast cancer, involved intracardiac injection of tumour cells into immunocompromised mouse models where tumours would subsequently form in the bone. It is important to remember that as these studies are performed in immunocompromised animals, the effects of tumour-elicited immune responses on the efficacy of bisphosphonate treatment are not evaluable. A number of the studies using human xenografts have employed two strategies for bisphosphonate delivery. Bisphosphonates were given after bone metastases had been established following intracardiac injection of breast cancer cells, termed "therapeutic dosing". Alternatively, bisphosphonate administration was prior to injection of tumour cells, and hence prior to establishment of bone metastases, termed "preventative dosing". Although osseous metastases appeared to be inhibited by both types of intervention with bisphosphonates, there were unexplained increases in soft tissue metastases in a number of studies when the preventative dosing strategy was followed [11–13]. This is similar to the effects seen in the clinical study by Saarto et al. [9] in which patients