Monitoring Response to Neoadjuvant Chemotherapy Using Pharmacokinetic Parameters

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Introduction Breast cancer patients who present with locally advanced breast cancer (LABC) are now routinely treated with neoadjuvant chemotherapy. In patients who achieve sufficient down staging appropriate surgery can be undertaken, either breast conserving surgery or mastectomy. Second line therapies are initiated in patients who do not achieve sufficient down staging. Traditionally treatment response has been assessed via tumour size measurement halfway through neoadjuvant chemotherapy.
The aim of this study was to determine if pharmacokinetic (PK) modelled parameters could predict response to neoadjuvant chemotherapy at an earlier time point than traditional tumour size measurements since physiological changes (vessel permeability, blood flow, etc) are expected to occur prior to size changes[1].

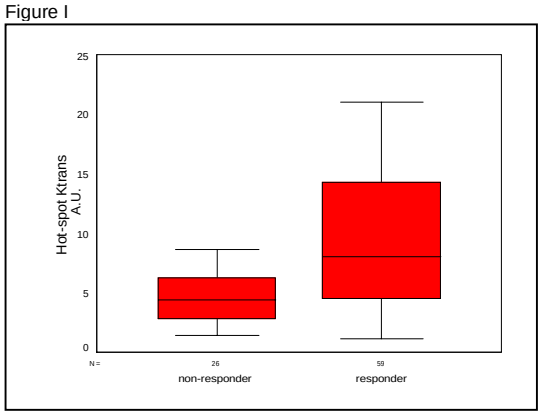
Methods Eight-five patients with LABC underwent magnetic resonance imaging on at least two time points, pre-treatment and after completion of treatment, additional MR imaging was performed after the 2nd cycle of treatment for seventy-nine patients. All MRI examinations were undertaken on a 1.5T scanner (GE Signa Advantage, GE Healthcare, Milwaukee, USA) in combination with a dedicated bilateral breast coil. Sequences comprised of 3D T1 weighted spoiled gradient echo (SPGR), proton density weighted SPGR, T1 weighted SPGR acquired dynamically over 35 time points with a typical temporal resolution of 11.6sec and a post contrast fat suppressed (FS) 3D T1 weighted SPGR. DCE-MRI images were analysed with in-house developed software on Sun workstations. A region of interest (ROI) was generated around the tumour on the slice which demonstrated the strongest contrast enhancement, a 3x3 pixel ROI was then generated from the original ROI, this is believed to represent the so called angiogenic hot spot of the lesion[2]. A two-compartment model (Brix)[3] was then applied to both ROI's to generate PK parameters transfer constant (K^{trans}), rate constant (K_{ep}) and extracellular extravascular space (V_e) for each ROI to describe the tumour vasculature. To classify patients as responders or non-responders ROI's were drawn around any enhancing lesion noted on the post contrast FS 3D T1 weighted SPGR images thereby providing a volume measurement. Patients were classified as responders based on a total tumour volume reduction of ≥65%, which equates to a 50% reduction in the product of a lesion's diameter, or non-responders based on a tumour reduction of <65%[4].

Results 26 patients were classified as non-responders and 59 patients were classified as responders. Table I presents the mean values for K^{trans}, K_{ep}, V_e and tumour volume for responders and non-responders for the pre-treatment and 2nd cycle time points. Significant differences between the response groups are also presented. Unlike volume PK parameters demonstrate a difference between the response groups prior to treatment. At the 2nd cycle time point only V_e and volume are significantly different. Additional paired sample t-tests revealed a significant reduction ($p < 0.001$) in K^{trans}, K_{ep} and volume for eventual responders while at the same time there was a significant increase ($p < 0.001$) in V_e for non-responders.

Table I

Parameter	ROI	Response Status	Pre-treatment		2nd Cycle	
			Mean	P value	Mean	P value
K^{trans}	Whole	Responder	6.66	*0.072*	5.14	NS
		Non-responder	4.40		3.36	
	Hot-Spot	Responder	11.16	**0.004**	7.02	NS
		Non-responder	5.75		7.03	
K_{ep}	Whole	Responder	3.58	NS	2.37	NS
		Non-responder	2.65		1.47	
	Hot-Spot	Responder	4.49	**0.021**	2.44	NS
		Non-responder	2.69		2.29	
V_e	Whole	Responder	1.96	*0.070*	1.85	**0.017**
		Non-responder	1.68		2.18	
	Hot-Spot	Responder	2.56	**0.023**	2.40	**0.023**
		Non-responder	2.07		2.87	
Volume	N/A	Responder	32.32	NS	15.81	**0.021**
		Non-responder	24.96		15.64	

Figure I



Discussion To be effective chemotherapy agents have to reach the target tumour cells via the patients vasculature. K^{trans} and K_{ep} represent vascular density, perfusion and endothelial permeability. Both of these PK parameter were higher for eventual responders prior to treatment. It is believed that the higher K^{trans} and K_{ep} parameters noticed in eventual responders prior to treatment reflected the greater blood, and therefore drug, delivery in these patients. Following the commencement of treatment there was a highly significant ($p<0.001$) reduction in both K^{trans} and K_{ep} in eventual responders, whilst in non-responders these parameters either decreased to a much lesser extent or even increased. V_e was lower for non-responders prior to treatment, restricting the volume accessible for chemotherapy agents. However V_e significantly ($p<0.001$) increased during treatment for non-responders, over the same time period V_e remained unchanged for responders. A transformation to a more malignant phenotype may explain the increasing V_e in non-responders. Both interstitial water space[5] and extracellular volumes[6] are similar to V_e and both have been shown to be higher in malignant tissues. It should be noted that volume was significant at the 2nd cycle stage and volume provided the greatest significant ($p<0.001$) difference between time points. However volume was not significant prior to treatment. Care should be taken in interpreting these results. While differences were demonstrated in PK parameters between response groups there was overlap in the results (see fig I) for all PK parameters. However these results do seem to suggest important differences in vascular density, perfusion, endothelial permeability and extracellular extravascular space between responders and non-responders both prior to and early during chemotherapy.

References [1]Padhani A..R. Eur J Cancer. 2002: **38** 2116-2127 [2]Liney G.P. et al. J Magn Reson Imaging. 1999: **10** 945-949 [3]Brix G. et al. J compu Assist Tomo. 1991: **15** 621-628 [4]Therasse P. et al. J Nat Cancer Inst. 2000: **92** 205-216 [5]Gullino P.M. et al. Cancer Research 1965: **25** 727-731 [6]Jakobsen I. et al. Magn Reson Imaging. 1995: **13** 693-700
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