Dynamic contrast-enhanced ultrasound (DCE-US) predicts outcome in patients receiving anti-vascular treatment for hepatic malignancy

Poster No.: C-1265
Congress: ECR 2015
Type: Scientific Exhibit
Authors: M. Abel, H. Wasan, E. L. Leen; London/UK
Keywords: Liver, Ultrasound, Contrast agent-intravenous, Cancer, Haemodynamics / Flow dynamics
DOI: 10.1594/ecr2015/C-1265

Any information contained in this pdf file is automatically generated from digital material submitted to EPOS by third parties in the form of scientific presentations. References to any names, marks, products, or services of third parties or hypertext links to third-party sites or information are provided solely as a convenience to you and do not in any way constitute or imply ECR's endorsement, sponsorship or recommendation of the third party, information, product or service. ECR is not responsible for the content of these pages and does not make any representations regarding the content or accuracy of material in this file. As per copyright regulations, any unauthorised use of the material or parts thereof as well as commercial reproduction or multiple distribution by any traditional or electronically based reproduction/publication method is strictly prohibited. You agree to defend, indemnify, and hold ECR harmless from and against any and all claims, damages, costs, and expenses, including attorneys' fees, arising from or related to your use of these pages. Please note: Links to movies, ppt slideshows and any other multimedia files are not available in the pdf version of presentations.

www.myESR.org
Aims and objectives

The liver is unique in that it has a dual blood supply, with approximately 75% coming from the hepatic portal vein and the remainder being delivered by the hepatic artery. It is also one of the most common sites of metastatic spread, second only to the lymphatic system. Heightened vascular signaling by cancerous cells result in angioneogenesis to promote tumour growth, which, in contrast to normal liver parenchyma, is almost exclusively arterial.

The introduction of biological agents has demonstrated a modest improvement in outcomes when used in certain malignancies [1-3]. By preventing the development of new vessels via inhibition of vascular pathways prominent in cancerous cells, their effects are cytostatic by reducing tumour perfusion and growth, unlike cytotoxic treatments designed to directly destroy malignant cells. Numerous therapies have been developed targeting pro-angiogenic mechanisms including the vascular endothelial growth factor receptors, platelet derived growth factor receptor, the mammalian target of rapamycin, c-Kit & Raf kinases.

Assessment of treatment response

The current gold standard in measuring response to anti-cancer therapy is the response evaluated criteria in solid tumours (RECIST). Comparison of tumour morphology grades outcomes as complete or partial response, stable disease or progressive disease [4]. Due to the cytostatic nature of anti-vascular treatments, their effects on tumour shrinkage may take considerable time to become detectable. Functional imaging may represent a more suitable monitoring option independent of tumour size.

Dynamic contrast-enhanced magnetic resonance imaging (MRI) or computed tomography (CT), as well as positron-emission tomography (PET) scans have been identified as possible alternatives to morphological tumour assessment, although limitations including availability, radiation exposure, expense and lengthy procedure times make these modalities unappealing for repeated imaging and long-term follow up [5-7].

Dynamic contrast-enhanced ultrasound (DCE-US)

The introduction of ultrasound contrast agents (microbubbles) within hepatic imaging has provided an additional modality for monitoring liver malignancy. As a purely intravascular tracer, microbubbles may be ideally suited to observing perfusion changes associated with a response to treatment [8].

Aim
The aim of this study is to assess whether perfusion changes using DCE-US in liver cancer patients receiving anti-angiogenic therapy predicts survival.
Methods and materials

Patient population

Twenty-five patients were recruited into the study prior to commencing treatment for primary or secondary hepatic malignancy with one of five biological agents including Aflibercept, Axitinib, Everolimus, Sorafenib and Sunitinib. Median age was 61 (range: 37-89). There were 15 males and 10 females.

Imaging protocol

DCE-US was carried out at baseline (# 7 days prior to first dose) and 2-weeks (± 2 days) after treatment initiation. Patients were supine and fasted for a minimum of 4 hours prior to scanning to eliminate post-prandial blood flow variations.

Sonovue (Bracco SpA, Milan, Italy) ultrasound contrast agent was reconstituted just prior to use as per the manufacturer's guidelines. A 2ml bolus was injected via a peripheral vein through a 20g+ cannula with attached 3-way tap. No further tubing or saline flush was used. DCE-US assessment was carried out in contrast specific mode with a curvilinear C5-1 transducer (iU22, Philips, Bothell, Washington, USA). Power modulation was used with a 1.7-MHz center frequency at a mechanical index of 0.06. The gain was set at 88% (default value) with the dynamic range at 50 dB (maximum value available). Time-gain controls were centered for all examinations. Procedure settings were set prior to the baseline scan with identical parameters applied for sequential scans. Ninety second cine-loops in a single plane visualising the hepatic artery and portal vein were acquired. An additional scan of the index tumour and adjacent normal liver parenchyma were obtained thereafter, once the previous contrast bolus was no longer visible.

Data analysis

QLAB software (Philips Ultrasound, Bothell, Washington, USA) was used for off-line post-procedure analysis on a desktop computer. Regions of interest (ROI) were drawn around the hepatic artery (HA), portal vein (PV), tumour (T) and adjacent normal liver parenchyma (L) to generate time intensity curves (TIC) (Figure 1). Respiratory gating was used to minimise influence of breathing motion.
Fig. 1: Single image from a 90 second video loop after Sonovue injection. Regions of interest depict the hepatic artery (red), portal vein (yellow), tumour (blue) and normal liver parenchyma (purple).

References: Imaging department, Imperial College, London, Hammersmith hospital - London/UK

TIC parameters including rise time (RT), peak intensity (PI), wash in slope (WIS) and area under the curve (AUC) were observed (Figure 2). Parameter ratios between hepatic artery and portal vein or tumour and liver parenchyma were calculated for normalisation purposes. Flow rate (FR) was defined as: PI x WIS. The contrast enhanced hepatic perfusion index (CEHPI), representative of the proportion of HA flow to global liver flow, was defined as: FRHA / (FR_{HA} + FR_{PV}).
Fig. 2: Image depicting indicative time intensity curves for the hepatic artery (red) and portal vein (yellow) including measured parameters.

References: Imaging department, Imperial College, London, Hammersmith hospital - London/UK

Progression free survival (PFS) was determined by follow up RECIST imaging scheduled under the individual control of the oncologists. Only hepatic tumour burden was considered. Patients showing complete/partial response or stable disease were defined as non-progressors (NPr); progressive disease was defined as a progressor (Pr).

Statistical analysis

Statistical analysis was carried out using a statistical software package (Prism; Graphpad Software, La Jolla, California, USA). Log-rank tests were used to determine correlations with PFS. Statistical significance was determined as p<0.05. Median follow up was 77 days (range: 47-475).
**Fig. 1:** Single image from a 90 second video loop after Sonovue injection. Regions of interest depict the hepatic artery (red), portal vein (yellow), tumour (blue) and normal liver parenchyma (purple).

© Imaging department, Imperial College, London, Hammersmith hospital - London/UK
Fig. 2: Image depicting indicative time intensity curves for the hepatic artery (red) and portal vein (yellow) including measured parameters.

© Imaging department, Imperial College, London, Hammersmith hospital - London/UK

PFS based on baseline tumour flow rate

Fig. 3: Graph depicting PFS based on baseline tumour flow rate.

© Imaging department, Imperial College, London, Hammersmith hospital - London/UK
**Fig. 4:** Graph showing PFS based on baseline liver flow rate.

© Imaging department, Imperial College, London, Hammersmith hospital - London/UK

**PFS based on baseline portal vein flow rate**

**Fig. 5:** Graph showing PFS based on baseline portal vein flow rate.
**Fig. 6:** Graph depicting PFS based on baseline CEHPI.

© Imaging department, Imperial College, London, Hammersmith hospital - London/UK
Fig. 7: Graph showing PFS based on liver flow rate changes by 2 weeks.

© Imaging department, Imperial College, London, Hammersmith hospital - London/UK
Results

At baseline, decreased PFS was associated with a higher flow rate in the index tumour (59 vs 107, p=0.004) (Figure 3), liver parenchyma (59 vs 101 days, p=0.015) (Figure 4) and lower portal vein FR (59 vs 101, p=0.047) (Figure 5).

**Fig. 3**: Graph depicting PFS based on baseline tumour flow rate.

*References*: Imaging department, Imperial College, London, Hammersmith hospital - London/UK
PFS based on baseline liver flow rate

![Graph showing PFS based on baseline liver flow rate.](image)

**Fig. 4:** Graph showing PFS based on baseline liver flow rate.

**References:** Imaging department, Imperial College, London, Hammersmith hospital - London/UK

PFS based on baseline portal vein flow rate

![Graph showing PFS based on baseline portal vein flow rate.](image)

**Fig. 5:** Graph showing PFS based on baseline portal vein flow rate.
A reduced CEHPI, representative of a smaller proportion of arterial flow relative to global liver flow, also correlated with worse PFS (74 vs 163 days, p=0.049) (Figure 6).

Fig. 6: Graph depicting PFS based on baseline CEHPI.

By 2 weeks, a greater than 30% decrease in liver FR was associated with worse PFS (59.5 vs 113 days, p=0.022) (Figure 7).
PFS based on liver flow rate changes by 2 weeks

Fig. 7: Graph showing PFS based on liver flow rate changes by 2 weeks.

References: Imaging department, Imperial College, London, Hammersmith hospital - London/UK
Conclusion

The aim of this clinical study was to assess the value of DCE-US as a potential new early surrogate biomarker to assess response to anti-vascular therapy in primary or secondary hepatic malignancy at tumoural and global liver levels.

Decreased PFS was correlated with increased arterial and liver parenchymal blood flow, as well as deceased portal vein flow at baseline. Also a higher arterial contribution to total liver blood flow was associated with worse outcomes. This may be explained by the neoangiogenic effect increasing the vascularity of the tumour, indicating more advanced disease.

During tumour driven angioneogenesis, vessel development is erratic and poorly controlled, leading to arterialisiation with vasculature that is physically and functionally pathological. Unsystematic and tortuous vessel arrangement, irregular permeability, pericyte malfunction, unpaired arteries and heterogeneous thickness within the basement layer contribute to an environment reducing treatment efficacy and promoting tumour growth [9]. The additional blood flow combined with continual expansion of the tumour further increases the pressure gradient between the tumour and vasculature [10]. A microenvironment of interstitial hypertension, hypoxia and acidaemia contribute to poor drug penetrance, tumour regression and inadequate immune cell access.

Although targeted at receptors prominent in malignant cells, vascular pathway receptors are also present in normal tissues. The association of shortened PFS with a reduction in liver parenchymal flow by 2 weeks may be due to unwanted effects of the anti-vascular treatment. DCE-US may be able to predict patients with excessive adverse reactions to cytostatic agents, which may enable prompt discontinuation of the drug or dose reduction strategies to improve tolerance. Liver reserve and the adverse consequences on healthy hepatic tissue may prove an equally valid marker for predicting survival.

The identification of pre-treatment perfusion parameters correlated with PFS can provide better treatment planning, potentially leading to reduction in medication administration costs, preventing drug-related adverse events and allowing earlier introduction of other treatments that may prove beneficial. In turn, this can improve survival and quality of life in liver cancer patients.

DCE-US used as a surrogate biomarker could also greatly expedite anti-vascular agent development. Phase 1 trials using RECIST end-points are currently required to use lengthy assessment schedules in order to grant new cytostatic agents sufficient time to produce a measurable difference in tumour morphology. Functional evaluation using
DCE-US could provide a suitable alternative that would more rapidly assess drug efficacy and guide clinical trial progress, delivering new therapies quickly and reducing the expense of drug development.

In conclusion, DCE-US measurement of tumoural and global liver haemodynamic changes may predict outcome in patients receiving anti-angiogenic therapy. DCE-US may be of use in routine clinical practice to predict outcomes in the treatment of hepatic malignancy with anti-vascular agents and to detect excessive adverse effects on normal liver parenchyma correlated with a worse outcome.
References


