Modelization of bevacizumab effect on tumour perfusion assessed by Dynamic Contrast Enhanced Ultrasonography

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Introduction

• Clinical efficiency of bevacizumab (Avastin®), an angiogenesis inhibitor, has been demonstrated in the treatment of solid tumours in association with classical chemotherapy[2]. The clinical use of bevacizumab would be improved if a predictive factor of its efficacy was established.

• Dynamic Contrast Enhanced Ultrasonography(DCEUS) is a medical imagery by ultrasonography which uses a contrast agent containing microbubbles (Sonovue®). This agent is strictly intravascular and its kinetics (intensity function of time) allows an assessment of tumour vascularisation[1].

Objectives

The aim of this work is to assess the role of Dynamic Contrast Enhanced Ultrasonography (DCEUS) as an early predictor of response to chemotherapy with bevacizumab

Data

• This study uses data from a clinical trial performed in the Hospital of Lyon (France).

• 13 patients with metastatic colorectal cancer, treated by 5FU, irinotecan, leucovorin and bevacizumab entered this study. The imagery analysis performed on the hepatic metastasis result in: 1/DCEUS: three curves of intensity at day 0, 21 and 49; 2/Scanner: 3 measures of tumour diameters at month 0, 2 and 4.

Methods

• The work is divided into two parts.

1-Modelling the sonographic intensity curve

• This model describes the intensity versus time curve I(t) and estimates hemodynamic parameters in tumour from this curve. The estimation is made for each patient at each examination time on the same metastasis. We use a multivessel model adapted from Krix and al[1]:

- $I(t)=I0 + Imax*exp(-ke.t)*v*t$, for $t \leq \tau$
- $I(t)=I0 + Imax*3/2*d*exp(-ke.t)*[1-d^2/(3.(v*t)^2)]$, for $t \geq \tau$

Where τ is the time for $I(\tau)=2/3*Imax$, v the blood velocity, Imax the maximum intensity (~ blood volume), I0 the basal intensity, d the width of the US beam and ke the elimination rate constant of Sonovue®. The secondary parameters are: blood flow f (≈ Imax*v) and perfusion P (≈ f/ Tumour volume). The model is fitted using *ADAPT II*®, the estimation procedure is the *Maximum Likelihood.*

2-Building a model able to predict the variation of the tumour size

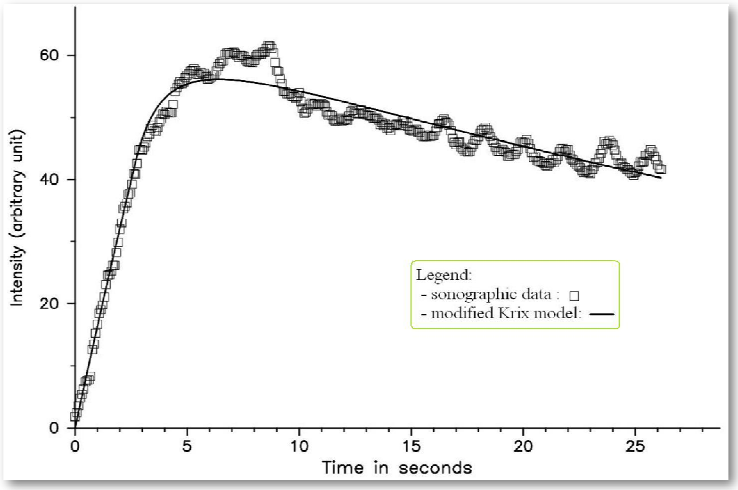
The second model is built by multivariate linear regression. The explicative variables are the estimated and secondary parameters from the intensity curve model, plus their relative variation between day 0 and day 21 or 49. The dependent variable is the tumour size variation at month 2 or 4.

Results

1-Estimation of hemodynamic parameters in tumour

• The modified Krix model fitted very well the sonographic data. The median tumoral perfusion at D0, D21 and D49 are 3.87E-02, 3.74E-02 and 4.38E-02 (arbitrary unit) respectively.

Graph 1 : Example of a modified Krix model 's fit



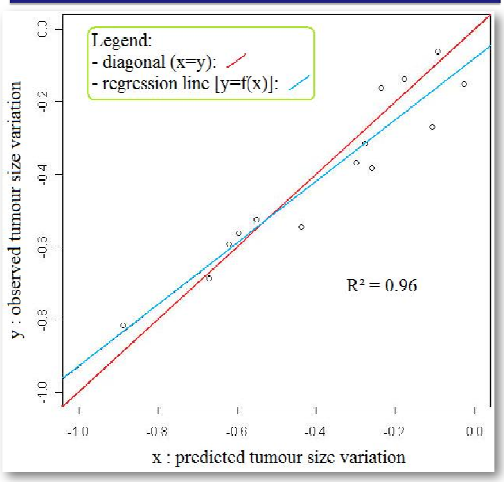
2-The predictive model of the tumour size variation

• The best predictive model incorporated Imax, perfusion, the variation of both blood flow and perfusion between D0 and D49 as variables to explain the relative variation of tumour size at M4:

Δtumour size = -0.0063*Imax + 0.19*P + 0.132*Δf - 0.098*ΔP

• Each parameter contributes significantly ($p < 0.05$) to the model with a standard error acceptable. The overall p value is < 10-6 and the R-squared is 0.96. No significant relation has been found between parameters at D21 and tumour size at M2 or M4.

Graph 2 : Visual validation graph of the tumour size variation model



Conclusion and perspectives

• A model able to predict early the treatment response by using a non invasive medical imagery was established. The analysis provided relevant information for understanding the pharmacological action of bevacizumab on metastatic vascularisation. The inhibitor of VEGF seems to reduce blood flow but to improve the action of associated chemotherapy by increasing the perfusion of the tumour.

References

[1] Krix M, et al. Ultrasound Med Biol. 2003; (10):1421-30
[2] Hurwitz H, et al N Engl J Med. 2004; 350(23):2335-42