BJC

British Journal of Cancer (2013) 109, 2024–2025 | doi: 10.1038/bjc.2013.498

Reply: Comment on 'Beta-blockers increase response to chemotherapy via direct anti-tumour and anti-angiogenic mechanisms in neuroblastoma' – β-blockers are potent anti-angiogenic and chemo-sensitising agents, rather than cytotoxic drugs

E Pasquier*[,1,2], N Andre[2,3,4], T Trahair[1,5] and M Kavallaris[1,6]

[1]*Children's Cancer Institute Australia, Lowy Cancer Research Centre, University of New South Wales, Randwick, NSW 2031, Australia;* [2]*Metronomics Global Health Initiative, Marseille 13005, France;* [3]*Aix-Marseille Université, Inserm, CRO2 UMR_S 911, Marseille 13385, France;* [4]*APHM, Hôpital Timone enfant, Service d'Hématologie et Oncologie Pédiatrique, Marseille 13385, France;* [5]*Sydney Children's Hospital, Randwick, NSW 2031, Australia and* [6]*Australian Centre for Nanomedicine, Chemical Sciences Building, University of New South Wales, Randwick, NSW 2052, Australia*

Sir,

We read with interest the comments from Ji and Chen (2013) on our recent publication providing evidence for the potential use of β-blockers in the treatment of neuroblastoma (Pasquier *et al*, 2013). This letter raised some interesting points and we agree that the effects of β-blockers on tumour endothelial cells and the role of adrenergic signalling in the biology of neuroblastoma both deserve further investigation.

Our work on the use of β-blockers for cancer treatment aroused from the serendipitous discovery of the efficacy of propranolol in treating severe infantile haemangioma (Leaute-Labreze *et al*, 2008). This finding led us to hypothesise that β-blockers may be able to increase the efficacy of chemotherapy against drug-refractory cancers, either through direct effects on cancer cells and/or *via* anti-angiogenic mechanisms. To date, we have screened the anti-angiogenic, anti-proliferative and chemo-sensitising properties of β-blockers alone and in combination with more than 10 different chemotherapeutic drugs in 17 different cell lines, including endothelial (4), breast cancer (3) and neuroblastoma cells (6) (Pasquier *et al*, 2011, 2013; and personal unpublished observation). We found that some β-blockers (i.e., propranolol, carvedilol and nebivolol) were consistently able to (i) inhibit angiogenesis *in vitro* and (ii) potentiate the anti-angiogenic and anti-proliferative effects of chemotherapy agents at concentrations that were 5- to 50-fold lower than those required to inhibit the proliferation of cancer cells when used alone. This goes to show that β-blockers are potent anti-angiogenic and chemo-sensitising agents, rather than true cytotoxic drugs.

In their letter, Ji and Chen (2013) focus their attention on the fact that β-blockers alone were able to slow down the growth of neuroblastoma tumours in TH-MYCN mice in our study. Although statistically significant, this anti-tumour effect did not translate into prolonged survival, indicating that this effect was transient. Importantly, the combination of β-blockers with vincristine increased the median survival of TH-MYCN mice up to 4-fold as compared with vincristine alone. These results were consistent with those observed with the combination of propranolol and paclitaxel in an orthotopic xenograft model of triple-negative breast cancer (Pasquier *et al*, 2011). Altogether, our compelling preclinical data indicate that β-blockers are more likely to be beneficial when used in combination with chemotherapy, rather than used as single agents.

One concern raised by Ji and Chen (2013) was the use of relatively high doses of β-blockers in our *in vivo* experiments. The doses used in this study were well tolerated by the animals, thus highlighting the inherent difficulties of extrapolating between doses used in animal studies and those effective in the clinic. Elsewhere, it is important to note that the use of standard doses of

*Correspondence: Dr E Pasquier; E-mail: e.pasquier@ccia.unsw.edu.au
published online 22 August 2013

β-blockers for the management of hypertension has been associated with clinical benefits in melanoma, breast, ovarian and non-small-cell lung cancer patients (Powe *et al*, 2010; Barron *et al*, 2011; De Giorgi *et al*, 2011; Lemeshow *et al*, 2011; Melhem-Bertrandt *et al*, 2011; Diaz *et al*, 2012; Wang *et al*, 2013). This clearly shows that β-blockers can be beneficial in cancer treatment, even when used at standard low concentrations. Higher doses may, however, be required to maximise the anti-cancer effects of β-blockers, which may lead to unwanted side effects such as hypotension and hypoglycaemia. Future clinical trials will therefore need to address the optimal dosage of β-blockers for a given clinical setting.

Finally, Ji and Chen (2013) highlighted a pertinent clinical perspective of our work. Recent clinical trials have focused on minimising treatment for patients with non-high-risk neuroblastoma and confirmed the excellent outcome of these patients (Hero *et al*, 2008; De Bernardi *et al*, 2009; Baker *et al*, 2010; Rubie *et al*, 2011; Strother *et al*, 2012). Many non-high-risk patients experience spontaneous tumour regression that may take up to 18 months to become evident (Hero *et al*, 2008). Unfavourable histopathology, tumour ploidy and genomics have emerged as important prognostic markers of increased risk of treatment failure, including in non-high-risk patients (Janoueix-Lerosey *et al*, 2009). These studies highlight the increasing importance of careful and refined risk stratification to determine the treatment approach for children with neuroblastoma. We caution against widespread use of β-blocker therapy in unselected, non-high-risk patients, most of whom have excellent clinical outcomes with minimal therapy. However, we advocate for the clinical investigation of the potential of β-blockers to (i) further reduce treatment intensity in selected non-high-risk patients with unfavourable prognostic features, (ii) improve outcome of non-high-risk patients who fail observation or recur after surgery and (iii) salvage patients with relapsed and/or drug-refractory neuroblastoma tumours. Furthermore, β-blockers may also prove useful in the context of cancer care in low- and middle-income countries, where multiple constraints call for the use of orally available, inexpensive drugs with low toxicity profiles (Andre *et al*, 2013).

REFERENCES

Andre N, Banavali S, Snihur Y, Pasquier E (2013) Has the time come for metronomics in low-income and middle-income countries? *Lancet Oncol* **14**: e239–e248.

Baker DL, Schmidt ML, Cohn SL, Maris JM, London WB, Buxton A, Stram D, Castleberry RP, Shimada H, Sandler A, Shamberger RC, Look AT, Reynolds CP, Seeger RC, Matthay KK. Children's Oncology Group (2010) Outcome after reduced chemotherapy for intermediate-risk neuroblastoma. *N Engl J Med* **363**: 1313–1323.

Barron TI, Connolly RM, Sharp L, Bennett K, Visvanathan K (2011) Beta blockers and breast cancer mortality: a population-based study. *J Clin Oncol* **29**: 2635–2644.

De Bernardi B, Gerrard M, Boni L, Rubie H, Cañete A, Di Cataldo A, Castel V, Forjaz de Lacerda A, Ladenstein R, Ruud E, Brichard B, Couturier J, Ellershaw C, Munzer C, Bruzzi P, Michon J, Pearson AD (2009) Excellent outcome with reduced treatment for infants with disseminated neuroblastoma without MYCN gene amplification. *J Clin Oncol* **27**: 1034–1040.

De Giorgi V, Grazzini M, Gandini S, Benemei S, Lotti T, Marchionni N, Geppetti P (2011) Treatment with beta-blockers and reduced disease progression in patients with thick melanoma. *Arch Intern Med* **171**: 779–781.

Diaz ES, Karlan BY, Li AJ (2012) Impact of beta blockers on epithelial ovarian cancer survival. *Gynecol Oncol* **127**: 375–378.

Hero B, Simon T, Spitz R, Ernestus K, Gnekow AK, Scheel-Walter HG, Schwabe D, Schilling FH, Benz-Bohm G, Berthold F (2008) Localized infant neuroblastomas often show spontaneous regression: results of the prospective trials NB95-S and NB97. *J Clin Oncol* **26**: 1504–1510.

Janoueix-Lerosey I, Schleiermacher G, Michels E, Mosseri V, Ribeiro A, Lequin D, Vermeulen J, Couturier J, Peuchmaur M, Valent A, Plantaz D, Rubie H, Valteau-Couanet D, Thomas C, Combaret V, Rousseau R, Eggert A, Michon J, Speleman F, Delattre O (2009) Overall genomic pattern is a predictor of outcome in neuroblastoma. *J Clin Oncol* **27**: 1026–1033.

Ji Y, Chen S (2013) Comment on 'Beta-blockers increase response to chemotherapy via direct anti-tumour and anti-angiogenic mechanisms in neuroblastoma' – β-blockers: a class of potential anti-neuroblastoma drugs. *Br J Cancer* **109**(7): 2022–2023.

Leaute-Labreze C, Dumas de la Roque E, Hubiche T, Boralevi F, Thambo JB, Taieb A (2008) Propranolol for severe hemangiomas of infancy. *N Engl J Med* **358**: 2649–2651.

Lemeshow S, Sorensen HT, Phillips G, Yang EV, Antonsen S, Riis AH, Lesinski GB, Jackson R, Glaser R (2011) beta-Blockers and survival among Danish patients with malignant melanoma: a population-based cohort study. *Cancer Epidemiol Biomarkers Prev* **20**: 2273–2279.

Melhem-Bertrandt A, Chavez-Macgregor M, Lei X, Brown EN, Lee RT, Meric-Bernstam F, Sood AK, Conzen SD, Hortobagyi GN, Gonzalez-Angulo AM (2011) Beta-blocker use is associated with improved relapse-free survival in patients with triple-negative breast cancer. *J Clin Oncol* **29**: 2645–2652.

Pasquier E, Ciccolini J, Carre M, Giacometti S, Fanciullino R, Pouchy C, Montero MP, Serdjebi C, Kavallaris M, Andre N (2011) Propranolol potentiates the anti-angiogenic effects and anti-tumor efficacy of chemotherapy agents: implication in breast cancer treatment. *Oncotarget* **2**: 797–809.

Pasquier E, Street J, Pouchy C, Carre M, Gifford AJ, Murray J, Norris MD, Trahair T, Andre N, Kavallaris M (2013) β-blockers increase response to chemotherapy via direct antitumour and anti-angiogenic mechanisms in neuroblastoma. *Br J Cancer* **108**: 2485–2494.

Powe DG, Voss MJ, Zanker KS, Habashy HO, Green AR, Ellis IO, Entschladen F (2010) Beta-blocker drug therapy reduces secondary cancer formation in breast cancer and improves cancer specific survival. *Oncotarget* **1**: 628–638.

Rubie H, De Bernardi B, Gerrard M, Canete A, Ladenstein R, Couturier J, Ambros P, Munzer C, Pearson AD, Garaventa A, Brock P, Castel V, Valteau-Couanet D, Holmes K, Di Cataldo A, Brichard B, Mosseri V, Marquez C, Plantaz D, Boni L, Michon J (2011) Excellent outcome with reduced treatment in infants with nonmetastatic and unresectable neuroblastoma without MYCN amplification: results of the prospective INES 99.1. *J Clin Oncol* **29**: 449–455.

Strother DR, London WB, Schmidt ML, Brodeur GM, Shimada H, Thorner P, Collins MH, Tagge E, Adkins S, Reynolds CP, Murray K, Lavey RS, Matthay KK, Castleberry R, Maris JM, Cohn SL (2012) Outcome after surgery alone or with restricted use of chemotherapy for patients with low-risk neuroblastoma: results of Children's Oncology Group study P9641. *J Clin Oncol* **30**: 1842–1848.

Wang HM, Liao ZX, Komaki R, Welsh JW, O'Reilly MS, Chang JY, Zhuang Y, Levy LB, Lu C, Gomez DR (2013) Improved survival outcomes with the incidental use of beta-blockers among patients with non-small-cell lung cancer treated with definitive radiation therapy. *Ann Oncol* **24**: 1312–1319.