Finally, we fully support Young et al's call to include discussions about fertility, early menopause and sexuality in the whole trajectory of cancer care. In order for this to realistically be possible alongside all the other important medical and contextual issues to be discussed, we need to allow health-care professionals a reflective space in which they can think about their own pressures and anxieties about discussing these difficult topics, be it time pressures, fear of emotional overload or worry that they cannot come up with feasible solutions.

We would agree with Young et al (2013) that timely information is crucial. We would also agree that Macmillan Cancer Care provides some of the most up-to-date, comprehensive and sensitively written cancer information available in the United Kingdom and would also wish to encourage oncologists and nurse specialists to share these materials with their patients. However, we feel that attention to those factors facilitating good communication are equally important. We ought to turn our attention to improving clinical communication, we owe it to patients and health-care professionals alike.

REFERENCES

Bar-Sela G, Lulav-Grinwald D, Mitnik I (2012) 'Balint group' meetings for oncology residents as a tool to improve therapeutic communication skills and reduce burnout level. J Cancer Educ 27(4): 786-789.

Fischer M, Ereaut G (2012) When Doctors and Patients Talk: Making Sense of the Consultation. Health Foundation: London.

Goodrich J (2012) Supporting hospital staff to provide compassionate care: do Schwartz Center Rounds work in English hospitals? J Royal Soc Med 105(3): 117-122.

Young N, Leibowitz A, Bowden R (2013) Comment on 'Fertility preservation in cancer survivors: a national survey of oncologists' current knowledge, practice and attitudes' - Oncologists must not allow personal attitudes to influence discussions on fertility preservation for cancer survivors. Br J Cancer 109(7): 2020.

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Comment on 'Beta-blockers increase response to chemotherapy via direct anti-tumour and anti-angiogenic mechanisms in neuroblastoma'

Y Ji*,1 and S Chen^{1,2}

¹Division of Oncology, Department of Pediatric Surgery, West China Hospital of Sichuan University, 37# Guo-Xue-Xiang, Chengdu 610041, China and ²Research Institute of Pediatrics, Children's Hospital of Fudan University, Shanghai 201102, China

We read with great interest the article published in British Journal of Cancer titled 'β-Blockers increase response to chemotherapy via direct anti-tumour and anti-angiogenic mechanisms in neuroblastoma' by Pasquier et al (2013). The study provided further evidence that β -blockers potentiated the anti-tumour and anti-angiogenic effects of vincristine in

neuroblastoma. Moreover, the data revealed that β -blockers significantly slowed neuroblastoma progression when used alone. We appreciate the authors' extraordinary contribution, which provides us with a pharmacological basis for the potential use of β -blockers in neuroblastomas. Nonetheless, there are several major points that need further discussion with respect to this article.

*Correspondence: Dr Y Ji; E-mail: jijiyuanyuan@163.com published online 22 August 2013







Angiogenesis is critical for cancer growth and progression. In the study by Pasquier et al (2013), the investigators found that treatment with vincristine or in combination with β -blockers significantly inhibited vascular structures by established endothelial cell (EC) lines (BMH29L cells). However, one major point on vincristine and/or β -blockers' mechanism of action is their specificity to cancer-derived ECs. It is well established that cancer-derived ECs show increased proliferation, motility, proangiogenesis properties and resistance to drug treatment compared with 'normal' ECs (e.g., HUVECs). For example, human breast cancer-derived ECs and human hepatocellular carcinoma tumourderived ECs exhibited increased resistance to vincristine and angiogenesis inhibitors (Grange et al, 2006; Xiong et al, 2009). A previous study also demonstrated that neuroblastoma-derived endothelial cells can originate from tumour cells and display MYCN amplification (Pezzolo et al, 2007). Therefore, the possibility that neuroblastoma-derived ECs are chemotherapysensitive warrants further investigation. Similarly, the effects of β -blockers on vascular structures have been previously shown (see Lamy et al, 2010), a major question is whether neuroblastomaderived ECs have more sensitivity to β -blockers. Thus, further experiments using both 'normal' ECs and neuroblastoma-derived ECs are needed to extend and confirm these findings.

Neuroblastoma is a clinical heterogeneous disease. In infants, it often presents as a localised adrenal mass. Although surgical resection is normally curative in these children, it can be associated with significant morbidity and mortality. Previous studies support the safety and effectiveness of the expectant observation (or 'wait and see') for localised infant neuroblastoma (Nuchtern et al, 2012). We were very much impressed that β -blockers alone could slow neuroblastoma progression in vivo. The safety and tolerability of β-blockers in young patients have been well documented (Drolet et al, 2013). Therefore, management of localised infant neuroblastoma with β -blockers can be used as a potential adjuvant treatment measure during the 'wait and see' period. However, the use of heroic doses of β -blockers in the study of Pasquier *et al* (2013) is of great concern. For instance, inhibition of tumour growth by propranolol (i.p. injections) occurred at a dose that was 10-50 and 500-5000 times those that used in paediatric patients during oral and intravenous treatment, respectively (Drolet et al, 2013).

 β -Adrenergic receptor (β -AR) signalling modulates key signalling pathways that are important for cancer-promoting processes. The neurotransmitters epinephrine and norepinephrine are the physiological agonists for β -ARs. These two neurotransmitters are catecholamines that are not only released from the adrenal medulla as a response to psychological and physical stress, but they also regulate cell and organ responses to the sympathetic branch of the autonomic nervous system. In many cases of neuroblastoma, elevated levels of catecholamines or their metabolites are found in the urine or blood (Nuchtern *et al*, 2012). Unfortunately, the potential role of the catecholamine-mediated activation of β -AR

signalling pathway in neuroblastoma pathogenesis (e.g., angiogenesis) has not been well investigated. It is known that agonist and antagonist of β -ARs act antithetic via the same intracellular pathways (Powe and Entschladen, 2011). As neuroblastoma cell lines derived from catecholamine-positive tumours retain the ability to produce and store catecholamines *in vivo* environment (Tomayko *et al*, 1996), do β -blockers exert their anti-neuroblastoma effects, at least partially, by inhibiting the effects of catecholamines? This question should be addressed by future research efforts.

REFERENCES

Drolet BA, Frommelt PC, Chamlin SL, Haggstrom A, Bauman NM, Chiu YE, Chun RH, Garzon MC, Holland KE, Liberman L, MacLellan-Tobert S, Mancini AJ, Metry D, Puttgen KB, Seefeldt M, Sidbury R, Ward KM, Blei F, Baselga E, Cassidy L, Darrow DH, Joachim S, Kwon EK, Martin K, Perkins J, Siegel DH, Boucek RJ, Frieden IJ (2013) Initiation and use of propranolol for infantile hemangioma: report of a consensus conference. *Pediatrics* 131: 128–140.

Grange C, Bussolati B, Bruno S, Fonsato V, Sapino A, Camussi G (2006) Isolation and characterization of human breast tumor-derived endothelial cells. Oncol Rep 15: 381–386.

Lamy S, Lachambre MP, Lord-Dufour S, Beliveau R (2010) Propranolol suppresses angiogenesis in vitro: inhibition of proliferation, migration, and differentiation of endothelial cells. Vascul Pharmacol 53: 200–208.

Nuchtern JG, London WB, Barnewolt CE, Naranjo A, McGrady PW, Geiger JD, Diller L, Schmidt ML, Maris JM, Cohn SL, Shamberger RC (2012) A prospective study of expectant observation as primary therapy for neuroblastoma in young infants: a Children's Oncology Group study. Ann Surg 256: 573–580.

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

Pezzolo A, Parodi F, Corrias MV, Cinti R, Gambini C, Pistoia V (2007) Tumor origin of endothelial cells in human neuroblastoma. *J Clin Oncol* 25: 376–383.

Powe DG, Entschladen F (2011) Targeted therapies: using beta-blockers to inhibit breast cancer progression. *Nat Rev Clin Oncol* **8**: 511–512.

Tomayko MM, Triche TJ, Reynolds CP (1996) Human neuroblastoma cell lines regain catecholamine fluorescence when xenografted into athymic (nude) mice. *Int J Dev Neurosci* 14: 771–777.

Xiong YQ, Sun HC, Zhang W, Zhu XD, Zhuang PY, Zhang JB, Wang L, Wu WZ, Qin LX, Tang ZY (2009) Human hepatocellular carcinoma tumor-derived endothelial cells manifest increased angiogenesis capability and drug resistance compared with normal endothelial cells. Clin Cancer Res 15: 4838–4846.

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