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.

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

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Sir,

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.

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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, pro-angiogenesis properties and resistance to drug treatment compared with 'normal' ECs (e.g., HUVECs). For example, human breast cancer-derived ECs and human hepatocellular carcinoma tumour-derived 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 chemotherapy-sensitive 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 neuroblastoma-derived 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.

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