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Letters

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Comments on: *Veno-occlusive Disease of the Liver in Right Sided Wilms' Tumours*, Tornesello *et al. Eur J Cancer* 1998, 34, 1220–1223

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WE READ with interest the paper recently published by Tornesello and colleagues [1] concerning the possibility of an increased risk of veno-occlusive disease (VOD) in patients with right sided Wilms' tumour (WT).

Hepatic VOD is primarily a clinical diagnosis based on criteria defined by McDonald. These criteria were probably not fulfilled by all the patients with liver toxicity reported in four different studies and included in the analysis performed by Tornesello and colleagues. For instance, only 2 of the 5 patients reported by Raine and associates [2] would meet the VOD criteria (3 children only had hepatomegaly and hypertransaminasaemia).

We earlier published data about hepatic toxicity in patients with WT treated according to the SIOP 9 protocol [3]. In this paper, VOD was defined according to the McDonald criteria [4]. Excluding patients enrolled by the German Paediatric Oncology Group, already included in the Tornesello analysis, and considering only non-irradiated children, we observed 21 cases of hepatotoxicity compatible with VOD in patients with unilateral WT. The tumour originated from the right kidney in 10 children. This was less than 50% of the patients.

Tornesello and colleagues presume that a long standing mass of the right kidney may cause obstruction of blood drainage of the liver. This may damage the intrahepatic vessels. Patients from the SIOP protocol received pre-operative chemotherapy and this usually led to a shrinkage of the tumour and consequently to the resolution of a hypothetical vascular compression. Hepatotoxicity was evident in our patients after a median time of 55 days (range 12–147). This means that in half of our patients toxicity occurred 2 or more months after initiation of chemotherapy. Vascular damage should have been less important by then.

We agree with Davidson and Pritchard [5] that hepatotoxicity in patients treated for WT is different from VOD in the setting of bone marrow transplantation even if all the criteria are met. Why children treated for WT are particularly at risk is not known. Actinomycin-D (AD) dose and schedule are considered risk factors, but the experience we had in the SIOP 9 study seems to indicate that younger age is more important ($P = 0.001$ in a multivariate analysis considering age, AD dose and radiotherapy). In particular, hepatotoxicity compatible with VOD was evident in 16% of children aged less than 1 year versus 6% in the older children.

Furthermore, we want to emphasise that the calculation of AD dose by patient weight instead of body surface led to a mean 25% reduction in the drug dose administered in our study, but this did not significantly protect children from VOD.

In conclusion, vascular compression from right sided WT should be considered in the analysis of future investigations, but it could not explain the occurrence of VOD in most of the patients considered in our study.

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Response from A. Tornesello, S. Mastrangelo and R. Mastrangelo

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WE WISH TO thank G. Bisogno and colleagues for their comments on our paper 'Veno-occlusive disease of the liver in right sided Wilms' tumours'. We agree with A. Davidson, J. Pritchard and G. Bisogno and colleagues that significant

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differences exist between the hepatotoxicity seen in Wilms' tumours (WT) treated with actinomycin D (AD) and that following bone marrow transplantation. Therefore, we feel that the criteria defined by McDonald [6] for veno-occlusive disease (VOD) in transplanted patients might not be applied strictly to VOD patients treated with AD for WT. For example, in the latter patients, a marked increase of liver enzymes has been frequently reported and this feature might well be included among the criteria for 'VOD' in WT patients. In any case, in Raine's series [7] there were only three right-sided WT out of a total of 5 VOD patients.

Bisogno and colleagues also state that tumours originated on the right side in less than 50% of their patients, but the overall evaluation of their series should also *include* the 7 cases, all with right-sided tumours, observed by the German Pediatric Oncology Group enrolled in the SIOP-9 nephroblastoma protocol [1]. Furthermore, whereas histopathological data in WT-VOD are rare and the WT-VOD diagnosis is ordinarily based on clinical findings, in 5 of the above 7 cases, liver biopsies were performed and confirmed clinical VOD [1]. With the addition of the 21 cases of WT-VOD now mentioned in the letter by Bisogno and colleagues to the 33 cases reported in the literature, children with right-sided WT still appear to develop 'VOD' more than twice as often as children with left-sided tumours.

In regard to the mechanisms leading to VOD in WT, mentioned by G. Bisogno and colleagues, we should like to further clarify our speculation. The venular endothelium appears to be the first site of injury when VOD occurs after radiation or when produced experimentally by pyrrolizine alkaloids [2–5]. The end result of the venular damage is the obstruction of sinusoidal blood flow, leading to ascites and hepatocellular necrosis. A similar type of injury may occur following only a few courses of AD, but with no clinical consequences, unless the venular endothelium is already somewhat damaged by a chronic partial blockade of the blood drainage of the liver, as caused by a right-sided WT. Thus, the shrinkage of the tumour and the resolution of the vascular compression within a few months would probably not be enough to prevent AD from causing VOD.

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Response from A. Davidson

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BISOGNO AND COLLEAGUES have reviewed their series of Wilms' tumours treated according to SIOP 9 protocol, originally published in 1997 [1], and found that there was no predominance of right-sided tumours in their patients who developed actinomycin-D related hepatopathy. This is in contrast to the findings of Tournesello and associates who found a marked excess of patients with right-sided renal tumours amongst those who developed actinomycin-D related hepatopathy, although these patients had been treated on a number of different protocols [2]. In the series reported by Bisogno and colleagues, only those patients with hepatoxicity who fulfilled the criteria of hepatic veno-occlusive disease (H-VOD) as defined by McDonald and associates were considered. However, there would not seem to be any logical explanation why this should alter the relative incidence of right versus left tumours developing the complication. Nor does it offer any alternative explanation of why patients receiving actinomycin-D for treatment of Wilms' tumours are so much more likely to develop hepatotoxicity than those receiving treatment for sarcomas.

Bisogno and colleagues also noted that actinomycin-D dose reduction did not influence the incidence of liver toxicity in their series. However, the experience from several other groups does suggest an increased risk when doses of more than 1.5 mg/m^2 or 45 μg/kg are used [3–5].

We are left with the following observations. Actinomycin-D hepatopathy is clearly more common in children treated with the drug for renal tumours; young infants are an increased risk; there is a probable dose effect and a possible laterality effect. One way of improving our understanding would be to improve our knowledge of actinomycin-D pharmacokinetics, especially in young infants. Limited pharmacokinetic studies in adults show a slow phase of plasma disappearance and a half-life of approximately 36 h, suggesting that there is likely to be accumulation after repeated administration. The drug is minimally metabolised, and probably around 10% of the drug is excreted via the biliary tree [6]. Although these observations were based on studies performed on only 3 adult patients, they lend weight to the suggestion that hepatic compression leads to delayed excretion after the first dose of actinomycin-D, and subsequent courses lead to progressive

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