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Editorial

Ifosfamide and Paediatrics: Should This Marriage Be Saved?

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PAEDIATRIC ONCOLOGY first met ifosfamide in the early 1970s, but the drug's disagreeable habit of causing haemorrhagic cystitis made the relationship a short one. With mesna as a chaperone, paediatric oncology was re-introduced to ifosfamide in the late 1980s, and they have seemed quite compatible: ifosfamide has displaced cyclophosphamide as front-line therapy for rhabdomyosarcoma in Europe, is seeking a place in osteosarcoma therapy in the United States, is used in many patients with a variety of relapsed tumours along with etoposide or in the appealingly-named 'ICE' (ifosfamide-carboplatin-etoposide) regimen, and is under evaluation in virtually every other paediatric tumour category.

As ifosfamide's role has increased, it has become clear that its long-term toxicity, particularly to the kidneys, threatens its continued role in paediatrics: patients can develop marked Fanconi syndrome, consisting of renal tubular acidosis, proteinuria, glycosuria, hyperphosphaturia with hypophosphataemia, and other urine and serum electrolyte abnormalities (see Skinner and associates [1] for review). While there are established risk factors for serious ifosfamide nephrotoxicity, including young age, previous exposure of the kidneys to cisplatin or radiation, hydronephrosis, a cumulative dose over 72 g/m^2, or a single kidney [1, 2], many patients not, by these criteria, at high risk still develop Fanconi syndrome, while others at high risk escape it.

Ifosfamide nephrotoxicity appears almost universal among children receiving the drug. In a thorough study in Dublin, O'Meara and colleagues found that 19 out of 20 patients studied had some renal abnormalities from ifosfamide, with five having "generalised nephrotoxicity" [3], which others would label Fanconi syndrome. Thus, almost every patient treated with ifosfamide has a renal abnormality, and although it is usually subclinical, the natural history, as patients survive and age, is unknown.

The nature of the nephrotoxicity also varies between patients experiencing it. For example, in the Dublin series, some patients had striking abnormalities in their ability to concentrate and acidify urine, but no electrolyte handling abnormalities, others had glycosuria and aminoaciduria with no other problems; 5 had Fanconi syndrome [3]. In some patients the renal lesion heals with time, while in others it appears to be a progressive nephropathy which may appear months after the end of therapy [2, 4].

This variability in nature and severity is the most frustrating aspect of ifosfamide nephrotoxicity. Boddy and colleagues report in this issue (pages 1179–1184) the latest in their excellent series of investigations of ifosfamide nephropathy. Their implicit hypothesis is that some patients have a pattern of ifosfamide metabolism which is associated with a higher risk of nephropathy; if one could identify those patients, one might avoid the nephropathy. Unfortunately, the hypothesis is not substantiated: "No correlation was seen between any measure of renal function and any of the parameters of IFO pharmacokinetics and metabolism. . .". The current report also reflects the great variation in metabolism and pharmacokinetics between individuals that others have reported. Boddy and colleagues have previously reported striking variations in ifosfamide pharmacokinetics and metabolism within individual patients, between different courses [5].

Thus, ifosfamide joins cisplatin and doxorubicin as common drugs in paediatric oncology which are highly effective, yet are burdened with largely unpredictable risks of serious late effects. Where ifosfamide differs from cisplatin and doxorubicin is in its replaceability. Cisplatin uniquely combines efficacy with minimal myelosuppression, and doxorubicin is the single most effective drug against a variety of tumours, particularly sarcomas. Ifosfamide, however, has a sibling in cyclophosphamide, which lacks the nephrotoxicity.

One must then ask, why use ifosfamide at all? Certainly the evidence for its efficacy is copious, particularly in sarcomas, but data showing superiority over cyclophosphamide are non-existent. The remarkable responses recorded in the last decade may simply be a function of dose: When ifosfamide was re-introduced, its doses (6 to 9 g/m^2 per cycle) were considerably more myelosuppressive than the contemporary doses of cyclophosphamide (generally 600–1200 mg/m^2 per cycle). If dose is important in the efficacy of alkylating agents, it is not surprising that ifosfamide should have seemed better. However, approximately 5 years ago, cyclophosphamide doses began to increase, and the Intergroup Rhabdomysarcoma Study Committee found that a single cyclophosphamide dose of 2.2 grams was almost equally myelosuppressive as 9 grams of ifosfamide given over 5 days [6].

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Using 90–165 mg/kg (2.7 to 5 g/m^2) of cyclophosphamide with etoposide, the Australian–New Zealand Childhood Cancer Study Group obtained responses in 10 of 12 evaluable patients with a variety of refractory and relapsed tumours [7], a response rate equalling those seen with ifosfamide-etoposide or ICE. In a non-randomised study in Ewing's sarcoma patients, Oberlin and coworkers found that those treated with vincristine-doxorubicin-ifosfamide had the same outcome as those treated with vincristine-doxorubicin-cyclophosphamide [8]. The Fourth Intergroup Rhabdomyosarcoma Study in the United States is comparing ifosfamide to cyclophosphamide in a randomised, head-to-head trial (vincristine-actinomycin-cyclophosphamide versus vincristine-actinomycin-ifosfamide versus vincristine-etoposide-ifosfamide). The doses of cyclophosphamide and ifosfamide were chosen to be equally myelosuppressive, although they are given on different schedules (ifosfamide as five doses of 1.8 g/m^2, cyclophosphamide as one dose of 2.2 g/m^2). Despite this and the statistical difficulty of demonstrating the equality of two regimens, this will provide valuable data.

Paediatric oncologists treat their patients with the hope that they will enjoy 60 or 70 more years of life. We tolerate substantial acute and chronic toxicities because survival is of paramount importance, but late effects can either truncate life or curse it with disease. As the assets and limitations of ifosfamide become clearer, and as more information comparing cyclophosphamide and ifosfamide becomes available, we need to re-examine its relationship with paediatric oncology. Perhaps it will not be a long and happy marriage after all.

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