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Review

An international strategy to determine the role of high dose therapy in recurrent Wilms' tumour

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KEYWORDS

Wilms' tumour Relapsed Wilms' tumour High dose chemotherapy **Abstract** *Purpose:* To review event-free (EFS) and overall survival (OS) from publications describing outcome for children with relapsed Wilms' tumour. Comparisons are made between those receiving myeloablative high dose chemotherapy with autologous stem-cell rescue (HDT) and those not (NoHDT).

Materials and methods: Relevant information was extracted from individual patient or summary data and 3-year EFS and OS rates established. These rates were combined in a weighted manner to derive hazard ratios (*HR*s).

Results: Nineteen publications were identified (5 HDT, 6 NoHDT, 8 both). Pooling all studies suggested an advantage to HDT with a hazard ratio (*HR*) for EFS of 0.87 (95% confidence interval (CI) 0.67–1.12) and 0.94 (0.71–1.24) for OS. A stratified analysis confined to studies that provided individual patient data on both HDT and NoHDT gave *HR*s of 0.83 (0.56–1.24) and 0.92 (0.59–1.41). Further, analyses of risk groups, defined by treatment and/or histology prior to first relapse, suggested a HR for EFS of 0.90 (95% CI 0.62–1.31) for those of high and 0.50 (CI 0.31–0.82) for the very high risk patients.

Conclusion: The evidence suggests, although there are many caveats since the information summarised here is not from randomised trials, a great deal of uncertainty concerning the role of

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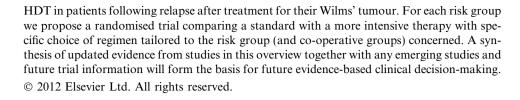
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1. Introduction

Wilms' tumour (WT) is the most common genitourinary tract cancer in childhood, with an annual incidence of 1 per 100,000 children.¹ Early recognition of the tumour's radiosensitivity and introduction of active chemotherapy agents in the 1960s improved survival rates to 90%.² Since the 1980s, multinational trial groups addressed the question of improving risk stratification of front line therapy to maintain these excellent survival rates whilst avoiding the risk of long term sequelae from doxorubicin and radiotherapy for the majority of patients.^{3–5}

The success of treatment of newly diagnosed WT presents challenges in determining optimum therapy for the small number of patients who suffer a recurrence. Before the mid 1980s, recurrent WT was treated with combinations of vincristine, actinomycin D, doxorubicin, radiation therapy or surgery. In many cases, identical chemotherapy agents were used for treatment of both primary and recurrent disease and long term overall survival (OS) rates for recurrent cases were poor at 24–43%. 6,7 Subsequently, more dose intensive second line combination regimens incorporating drugs such as cyclophosphamide, ifosfamide, cisplatin, carboplatin and etoposide have been shown to be efficacious, but their impact on long-term survival remains poorly defined.^{6–9} Due to poor long-term survival rates, several groups have incorporated myeloablative high dose chemotherapy into relapse regimens. 8,10-12 However, no randomised comparison of the potential additional benefit of such an approach over systematically intensifying non-myeloablative chemotherapy has been concluded.

The application of risk-adapted intensive retreatment strategies has improved survival after relapse of WT to nearly 80% for the subgroup who relapse after minimal first line therapy consisting of only vincristine and actinomycin D. However, nearly two thirds of relapses fall into higher risk groups that have received prior treatment with doxorubicin and, sometimes, with radiotherapy and additional chemotherapeutic agents. Nevertheless approximately half of these 'high risk' relapses can be salvaged with a combination of intensive multiagent chemotherapy, together with surgery and radiotherapy where feasible. ^{10,13}

An international consensus is forming on the approach to risk stratification of relapsed WT. ^{11,12} There is recognition of three groups: standard, high and very high risk; according to initial treatment received, which in turn is largely dictated by tumour stage and histology. Clinical relevance of other putative prognostic factors such as time to

relapse and site of recurrence is less certain. 14,15 The standard risk group, who relapse after vincristine and actinomycin D in first line therapy, are generally salvageable. Current approaches using fairly intensive dose and scheduling of different chemotherapy agents to those used first line (usually based on combinations of doxorubicin, ifosfamide/cyclophosphamide, etoposide and sometimes carboplatin) combined with routine use of radiotherapy and surgery of relapse site where feasible, achieve second 3-year event free survival (EFS) of approximately 80%. 10,16 However, high- and very-high-risk relapse groups present two areas of specific clinical need. The first need is to define the role of myeloablative high dose chemotherapy in treatment of relapse occurring after therapy including doxorubicin and/or radiotherapy (high-risk) where survival rates of approximately 50% are reported with systemic use of intensive chemotherapy. ^{10,13} Second is to identify more efficacious treatments for tumours with initial high risk histology (anaplastic or pre-treated blastemal type) or adverse molecular characteristics that recur or progress after first line intensive multiagent therapies and have very poor outcomes (very-high-risk group).

Given that most relapsed WT patients already have some degree of renal compromise and will be receiving nephrotoxic drugs at relapse, there is an important clinical question about whether high dose chemotherapy requiring ASCR (autologous stem-cell rescue) is able to increase overall survival. Retreatment with intensive but non-myeloablative chemotherapy would theoretically lower the risk of morbidity and mortality and long-term renal dysfunction.

The objectives of this paper are to review historical evidence for anticipated 3-year EFS and OS rates after relapse in WT, to quantify how outcome depends on intensity of pre-relapse treatment received and to investigate whether a retreatment approach using high dose therapy with ASCR should be tested in those of poor prognosis following their relapse. As a consequence of this review a flexible randomised trial to address the role of high dose therapy using intensive multidrug regimens for treatment of relapsed WT is proposed.

2. Materials and methods

2.1. Types of studies included

All studies that investigated treatment of relapsed WT using intensive chemotherapy with or without high dose chemotherapy and ASCR, and provided individual patient, graphical or summary data, on EFS and/or OS.

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