

High dose therapy for recurrent Wilms' tumor

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Abstract: The prognosis for most patients with newly diagnosed Wilms' tumor (WT) is excellent, but those who have recurrent or refractory disease have a significantly worse prognosis. High dose chemotherapy (HDT) requiring autologous stem-cell rescue has been tried for recurrent WT with variable results, but no randomized clinical trial has ever been performed. A recent review by T.C. Ha and colleagues of the published cases to date suggests HDT may be beneficial to the very high risk subset of patients with recurrent WT, but this conclusion is fraught with the caveats of any retrospective review. A prospective clinical trial would be challenging to complete but with careful planning and international collaboration it could be accomplished. Such a trial is likely the only way to know with certainty the safety and efficacy of HDT for recurrent WT.

Keywords: Wilms' tumor (WT); relapse; recurrent; high dose chemotherapy (HDT); autologous stem-cell rescue

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Wilms' tumor (WT) represents approximately 95% of pediatric renal tumors and generally has a favorable prognosis, with an overall survival (OS) rate of approximately 90%. Current clinical trials largely use risk adaptive therapy to optimize OS while attempting to minimize the late effects of treatment. For newly diagnosed patients, current risk stratification factors used by the Children's Oncology Group include age, stage, tumor weight, histology, degree of lung nodule response to initial therapy, and loss of heterozygosity (LOH) on chromosomes 1p and 16q. Gene expression analysis is also being studied to further refine stratification of risk (1).

The first line treatment of WT involves surgery in every case, chemotherapy in the vast majority of cases, and radiation therapy in a minority of cases. Vincristine and dactinomycin are the most commonly used chemotherapy agents for lower risk patients and serve as the backbone for more intensive regimens. More intensive chemotherapy is indicated for higher risk patients (typically those with Stage III disease with LOH of 1p and 16q, and Stage IV disease), including doxorubicin, cyclophosphamide, and etoposide; and radiation therapy is also used in most high risk cases.

Up to 25% of newly diagnosed patients will have

refractory or recurrent disease, and the prognosis for these patients is significantly worse than newly diagnosed patients. With modern therapies, 40-70% of patients who relapse after initial treatment for unilateral WT can be salvaged (2-5). Many patients who relapse the first time can be cured with second line chemotherapy and radiation therapy, without high dose chemotherapy (HDT) including autologous stem cell rescue. However, some patients relapse again or remain refractory to therapy and may ultimately require more aggressive therapy. Patients who relapse can generally be risk-stratified into three subgroups: standard, high, and very high. Reported adverse prognostic factors include higher initial stage, the number and types of chemotherapy agents used prior to relapse, unfavorable histology, shorter first remission, relapse at more than one site, and a subsequent relapse or progression after a first relapse (2,6). It is for these patients that more effective therapies are urgently needed.

HDT followed by autologous stem-cell infusion has been tried for a number of pediatric malignancies with mixed results. It is part of the standard front-line therapy for high risk neuroblastoma, and is an accepted treatment strategy for selected cases of recurrent lymphoma. Its role

in recurrent leukemia is limited, mostly by the use of more intensive chemo-radiation treatments as well as allogeneic transplants. HDT has been used with variable outcomes for several other pediatric malignancies including WT, relapsed sarcomas, brain tumors, germ cell tumors, and retinoblastoma (7).

Like the majority of pediatric solid tumors (neuroblastoma being the exception), no randomized trial has been done to compare HDT versus no HDT for recurrent WT, and it is this fact Ha *et al.* address in their article "An international strategy to determine the role of high dose therapy in recurrent Wilms' tumour" recently published in the *European Journal of Cancer* (8). The authors' objectives were to "review historical evidence for anticipated 3-year event-free survival (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 autologous stem cell rescue should be tested in those of poor prognosis following their relapse". The authors do an outstanding job of reviewing the published literature and note that their work is not a meta-analysis, because no randomized clinical trials have yet been done. Rather, it is a review and carefully crafted proposal which addresses a controversial issue in pediatric oncology.

After a clearly defined and comprehensive search, the authors reviewed 19 relevant publications. Of the 19 publications, five reported the results of patients treated with HDT, six without HDT, and eight reported results for both. Studies were further classified and weighted according to size, year of publication, quality of data, and patient characteristics. Overall three-year EFS and OS were calculated using well established statistical methods. The pooled data suggest a benefit from HDT, especially for those of the very high risk group based on stage, histology, initial treatment received, and prior relapse. For patients with standard and high risk relapse (as opposed to very high risk), the benefits of HDT are much less clear, and in some cases HDT may be more harmful than helpful. A previous review of many of the same studies also suggested that HDT may be most effective for high stage patients with a lung-only relapse, and that HDT may not be beneficial for other subgroups (4). Ha *et al.* propose an international randomized trial to compare a more intensive regimen (i.e., HDT) to a standard treatment regimen (i.e., without HDT) for patients with relapsed/refractory WT in the high and very high risk subgroups.

Almost without exception, randomized clinical trials are

powered to answer at least one specific question. In this instance, however, the authors make an interesting case for a randomized trial which may not in itself definitively answer the question of whether HDT is beneficial or not to patients with recurrent WT. They recognize the infeasibility of a trial which would accrue enough high and very high risk patients in a defined period of time to clearly answer the question. Instead, they propose enrolling and randomizing "as many patients as possible over a reasonable time-frame (say 3-5 years)". The results generated from such a trial could then be combined with the results presented in their review (updated, if possible) to form "an improved level of certainty in the evidence base".

This is an ambitious proposal on many levels, and several obstacles will need to be navigated to open and complete such a trial. Some obvious obstacles include the need for international cooperation between pediatric oncology and stem cell transplant groups, the logistics of communication and planning, and the costs of funding such a trial; but there are scientific obstacles as well.

The molecular genetics of WT are complex, with multiple genes implicated including *WT1* (on chromosome 11p13), *WTX* (on chromosome Xq11.1), *CTNNB1* (the gene encoding β -catenin, on chromosome 3p22.1), and *IGF2* (on chromosome 11p15) (1,9). A gain of chromosome 1q has recently been shown to be an unfavorable marker for patients with favorable histology WT (1). In addition, a WT "stem cell" has been proposed (10). These genes and "stem cells" are potential therapeutic targets (10-12), and clinical trials using new agents aimed at these targets would reduce the number of patients eligible for a HDT trial.

Based on the principles of HDT, minimal disease states will likely be required for optimal outcome. Therefore the disease status prior to HDT could complicate any trial design, particularly if patients have measurable disease prior to HDT. Most patients will not have completely normal scans secondary to prior therapy. Residual scarring, pleural thickening, nonspecific pulmonary nodules, and borderline enlarged lymph nodes are all common after therapy for WT. Should those lesions be resected or biopsied and, if so, when (before or after HDT)? If the lesions are positive for tumor pre-HDT, should such a patient proceed with HDT anyway? Another factor that will be challenging to control is radiation therapy, which can be administered before or after HDT. Many of these patients will have received radiation therapy in the past, and it may be challenging to develop consistent guidelines for fields and doses.

Would relapse chemotherapy be standardized prior

to HDT and, if not, how would the different treatment regimens be analyzed? Ifosfamide/carboplatin/etoposide, cyclophosphamide/etoposide, and carboplatin/etoposide are commonly used salvage regimens (6).

Almost all of these patients will have only a single kidney, so HDT conditioning regimens should attempt to minimize nephrotoxicity (as the authors note). Renal dysfunction is indeed common in this circumstance, but is generally temporary and manageable (13). But could one convince transplant physicians to give a common conditioning regimen? A higher number of conditioning regimens will make confident conclusions difficult to discern.

The collection of peripheral blood stem cells (PBSC) is generally safe and feasible, even in young children, although up to 20% will have fewer than the targeted dose (14). If autologous PBSC harvest is unacceptably low, would allogeneic transplant be considered? Matched unrelated cord blood has been used at least once successfully for refractory WT, albeit with relatively short follow up (two years) (15).

Another large barrier to conducting a successful study will be getting physicians and families to “buy in” to a randomized clinical trial of HDT versus no HDT. Smaller institutions may decline opening such a trial due to the regulatory burden required and the relatively small number of eligible patients anticipated at any given institution. Individual investigators and institutional review boards would need to be educated and convinced of the value of such a trial. If one is already a “believer” in HDT, this bias may influence the advice given to families, or even the decision to open the trial at any given institution. Because of the current lack of a randomized trial, many physicians would not advocate HDT as a “standard” treatment for recurrent WT, whereas others may already consider HDT as the standard, or at least an acceptable, option for some patients. Ironically, the results shown by Ha *et al.* that HDT may most benefit patients in the very high risk subgroup may be used to justify not supporting a randomized trial, despite the uncertainty and caveats clearly discussed by the authors.

Finally, perhaps the biggest obstacle of all will be obtaining parental consent. Parents may have misgivings about enrolling their child onto such a trial. A common misconception about cancer therapy is that “more is better”, particularly in the relapse setting, and some parents may not feel comfortable allowing their child to have second line chemotherapy and radiation therapy, and possibly “missing out” on the potential benefits (albeit with risks, too) of HDT. If consent and assent are obtained and the

child is randomized to the no-HDT arm, some parents may withdraw consent and request HDT off study. This scenario would compromise the integrity of the trial and also place physicians in a quandary.

Despite these obstacles, an international randomized trial assessing the role of HDT for recurrent WT is the only way to answer the question. Even though the proposed trial may not in itself definitively answer the question, it would go a long way when combined with other available data. Pediatric oncology and pediatric transplant groups have a favorable history of collaboration, and have consistently been lauded as a model for other cooperative groups. The fact that this paper’s authors span three continents (Asia, North America, and Europe) is a telling example of how international collaboration can be achieved. The foundation for a trial laid by Ha and colleagues is a critical first step. The next step should be accomplished in a timely fashion, before the complexities of the world economy, regulatory burden, and human psychology get in the way.

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Footnote

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