Treatment of Relapsed Wilms Tumor Patients

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A. Introduction

The treatment outlook for children with the newly diagnosed Wilms tumors (WT) has improved substantially with the advent of modern therapy, which includes surgery, chemotherapy, and, in select cases, radiation therapy. Survival rates are currently approaching 90% and 1/3 the overall long-term survival of patients with relapsed disease remains at approximately 50%. Due to the small numbers of patients with relapsed WT, advances in treatment have remained a challenge. Because most reported studies either deal with a small prospective cohort of patients or are retrospective in nature, only limited conclusions can be drawn from this data. Therapy for patients with relapsed WT
depends on the characteristics of their primary disease, extent of previous therapy, and time elapsed from the initial diagnosis to relapse.

A. References


B. Risk Stratification for Patients with Relapsed Wilms Tumor

Different potential prognostic features that influence outcome post-relapse have been analyzed; however, it is difficult to determine whether these factors are independent. Moreover, the prognostic factors appear to be changing over time as therapy for primary and relapsed WT evolves.

Grundy et al performed the first comprehensive review of prognostic factors in children with relapsed WT in patients who had enrolled on the National Wilms Tumor Studies (NWTS)-2 and -3. They indicated that time to recurrence was predictive of survival, with those patients who relapsed early (0–5 months from nephrectomy) having worse outcomes than those who relapsed after more than 6 months. Other adverse prognostic factors were anaplastic histology, tumor stage III/IV, and relapse outside the lung. A more recent report from the NWTS-5 showed that the time to relapse and the site of relapse were no longer associated with poor prognosis. In addition, a group of patients who were initially treated with 2 drugs (i.e., vincristine [V] and
dactinomycin [A]) fared better than patients who were initially treated with 3 drugs (V and A plus doxorubicin), indicating that the initial treatment remains a significant prognostic factor.

Pein et al, in a review of the International Society of Pediatric Oncology (SIOP) WT studies, identified the following prognostic factors associated with worse outcomes after relapse: initial stage IV disease, anaplastic histology, time to recurrence 6 months or less after diagnosis, recurrence in multiple organs, or recurrence in a previously irradiated field. The German group analyzed a cohort of 170 relapsed patients and like other studies, determined that the initial stage III or IV, high-risk histology (including blastemal-type tumor after preoperative chemotherapy according to the SIOP classification), early relapse, combined with the site of were prognostic indicators associated with poor outcome.

A possible explanation for the differences in outcomes between pulmonary and abdominal relapses may be due to the fact that many abdominal recurrences occur in irradiated fields, whereas most lung recurrences develop in non-irradiated sites. Furthermore, when referring to “lung” or “abdominal” relapses, the reports do not distinguish between different categories (i.e., lung = pulmonary parenchymal relapses or mediastinum; abdominal = tumor bed (kidney area), retroperitoneal lymph nodes, liver, peritoneum, or contralateral kidney. For these reasons, the site of relapse deserves more analysis before being definitively considered for patient risk grouping. However, it is likely that the factors that were originally identified as having a prognostic value for survival, like the site of relapse or time taken for relapse, may lose their significance when more aggressive and effective regimens are adopted. Furthermore, the changes in the first-line disease therapy are now evolving towards less intense initial treatment for patients with lower disease stages and favorable histology. Intensification for patients with advanced disease, presence of metastases, and/or unfavorable histology may not only lead to a decrease in
the number of relapses but may also influence the outcome after relapse. The more selective upfront use of radiation in the recent era may allow for increased use of radiation at relapse, contributing to the improved patient outcome.

In summary, the features that seem to be clearly associated with a worse outcome after relapse are as follows: anaplastic or SIOP high-risk histology (i.e., blastemal-type WT) and initial chemotherapy with drugs, including doxorubicin. On the other hand, it is less clear whether time to recurrence remains associated with a poor outcome in contemporary therapy.

Based on previous considerations and data, 3 risk categories for recurrent WT can be schematically identified:

1) **Standard risk**: defined as patients with favorable histology WT who relapse after therapy with only V and/or A. This group accounts for approximately 30% of all relapses. These patients are expected to have an event-free survival (EFS) between 70–80%, as reported by the NWTS-5, and the United Kingdom Children’s Cancer and Leukemia Group (UKCCLG).3,7

2) **High risk**: defined as patients with favorable histology WT who relapse after therapy that utilizes at least 3 or more agents (including doxorubicin). These patients account for 45–50% of the children with relapsed WT. Their expected EFS is between 40–50%.2

3) **Very high risk**: defined as patients with recurrent anaplastic or post-chemotherapy blastemal-type WT. This group accounts for 10–15% of all WT relapses. These patients have dismal overall survival (OS) of less than 10%.6,8
B. References


C. Principles of Treatment

In general, most patients with relapsed WT are treated with a multimodal approach that includes chemotherapy, surgery, and radiotherapy. Although, we will discuss general guidelines for therapy, unless patients are enrolled on a clinical therapeutic study, therapy should take into consideration previous disease characteristics as well as exposure to previous therapeutic modalities, i.e., surgery and/or radiotherapy.

C.1 Surgery

The indications for, timing of, and modalities of surgery in children with relapsed WT are rarely addressed, and it is difficult to standardize a surgical approach for patients with relapsed tumors. Most of the information we have gathered on surgery is extrapolated from unselected groups of patients or case discussions. Surgical resection of operable-relapsed tumors is probably helpful, but its role has not been examined or validated prospectively.

The lack of data on the surgical excision of lung metastases in relapsed patients precludes precise interpretation of its potential role. Green et al, in a retrospective review of the NWTS group experience, suggested that the surgical removal of all pulmonary metastases is unlikely to improve post-relapse survival as compared with treatment with whole-lung radiation therapy and chemotherapy.¹ In a more recent retrospective analysis, Dome et al reported that patients who underwent complete surgical resection of their relapsed tumor had a higher probability of survival than patients who had incomplete resection or did not undergo any surgery.²

German data on the surgical aspects of liver metastases or relapse suggested that complete surgical resection of the diseased portion of the liver improves survival. Fuchs et al reported that children with a relapse in the liver...
who had complete resection of the tumor survived, while all patients with an incomplete resection died of the disease.\(^3\) It is important to note that in this report, patients who achieved complete remission following chemotherapy and/or hepatic resection did not receive radiation therapy to the liver.

Overall, it is tempting to speculate that surgery likely plays an important role in treating WT relapses; however, we cannot exclude the fact that patients who underwent a complete surgical resection had less aggressive or extensive disease.

C. References


D. Radiation Therapy

Comparatively, the indications for and doses of radiation therapy for newly diagnosed patients with relapsed WTs have not yet been investigated in a uniform fashion. While administration of radiotherapy to a previously non-irradiated field is consistently used and is possibly associated with a higher probability of survival, the indications for irradiation at a previously irradiated site of relapse, which is not a rare situation, remains controversial.

Uniform guidelines for radiation therapy were developed for the NWTS-5 relapse study and included higher doses than those used at initial diagnoses, even if the primary therapy did not include radiotherapy.\(^1,2\) Given the heterogeneity of clinical situations and the lack of data on the systematic use of
radiotherapy, the indications for the use of radiotherapy and the appropriate
doses to be delivered for patients with relapsed WT, who previously received
radiation therapy, remains controversial. Treatment plans for these patients
should be created cooperatively with a radiation oncologist and should take
into consideration the response to chemotherapy, extent of surgical resection,
and consideration for the use of high-dose chemotherapy with stem cell rescue,
since severe pulmonary toxicity following high-dose chemotherapy has been if
radiotherapy is delivered earlier. In general, the recommendation is to postpone
lung irradiation until after autologous stem cell rescue (ASCR).

D. References

1 Malogolowkin M, Cotton CA, Green DM, et al. Treatment of Wilms tumor relapsing after initial
treatment with vincristine, actinomycin D, and doxorubicin. A report from the National Wilms
treatment with vincristine and actinomycin D: a report from the National Wilms Tumor Study

E. Chemotherapy

The efficacy of ifosfamide (52% objective responses),1 etoposide (42% responses)2 and carboplatin (52% responses)3 either as single agents or in
combination4,5 for the treatment of relapsed WT has been evaluated in
prospective phase II studies. More recently, colleagues from St. Jude Children’s
Research Hospital investigated the activity of topotecan (48% responses) in
patients with favorable histology WT.6

In a review involving 54 patients who enrolled in consecutive trials at St.
Jude Children’s Hospital, Dome et al demonstrated that the outcome for
patients with relapsed WT has improved significantly since around the mid-
eighties, when alkylating agents, platinum compounds, and etoposide became
available.\textsuperscript{7} The introduction of these drugs led to disease-free survival (DFS) rates in children with relapsed WT in the range of 50–70%. Nevertheless, the best combination, dose-intensity, and duration of chemotherapy remain to be explored in a prospective and randomized clinical trial. In the following section, the authors try to summarize the most up-to-date recommendations to treat recurrent WT patients according to their risk at relapse.

E. References


F. Standard-risk Relapsed Wilms Tumor

Children with an initial low-stage, favorable histology WT have excellent survival rates with minimal therapy; therefore, the number of patients matching the criteria defining standard-risk relapsed tumors is very small, accounting for approximately 30% of all relapses. There is a paucity of reports focusing selectively on this patient population. Green \textit{et al} reported the outcomes in 58 children who relapsed after an immediate nephrectomy (stages I and II), initial
chemotherapy with V and A, and no radiation therapy (low risk) and were registered on stratum B of the NWTS-5 relapse protocol. Relapsed treatment included surgical excision when feasible, radiation therapy, and alternating courses of V, doxorubicin, cyclophosphamide and etoposide, and cyclophosphamide. The 4-year EFS and OS was 71.1% and 81.8%, respectively, for all patients and 67.8% and 81.0%, respectively, for those who relapsed only in their lungs. This survival rate appears to be improved compared to a crude survival rate of 57.9% among 19 children with stage I or II and favorable histology WT who relapsed after treatment in the United Kingdom Children's Cancer and Leukemia Group (UKCCLG) protocol for relapsed WT or compared to the 47.8% 5-year overall survival rate for children with relapsed stage I or II and favorable or anaplastic histology reported by investigators from St. Jude Children's Research Hospital.

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**F. References**


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**G. High-risk Relapsed Wilms Tumor**

More recently reported series, ranging between 11 to 60 patients with seem to support the rationale for dose-intense strategies, though a consensus has not yet been reached on whether high-dose chemotherapy with ASCR can account for improvement in outcome.
G.1 Conventional-dose Chemotherapy

Abu-Gosh first et al reported 11 children with high-risk relapsed WT treated with ifosfamide, carboplatin, and etoposide (ICE) chemotherapy and obtained a 63.6% EFS and OS at 3 years, although almost all received additional therapies, including surgery, radiation, or other chemotherapy drugs. Doses for the ICE course were as follows: ifosfamide, 1800 mg·m^{-2}·d^{-1} × 5 days; carboplatin, 400 mg·m^{-2}·d^{-1} × 2 days; and etoposide, 100 mg·m^{-2}·d^{-1} × 5 days. The ICE regimen was demonstrated to be extremely efficacious in determining second responses (82% objective response rate).

It is significant because persistent nephrotoxicity was moderate, as noted by other groups.\(^2,3\)

Malogolowkin et al reported for the NWTS-5 relapse protocol 60 homogeneously treated children who relapsed after an initial therapy with V, A, and doxorubicin plus radiotherapy.\(^4\) The 4-year EFS and OS were 42.3% and 48%, respectively, for all patients and were 48.9% and 52.8%, respectively, for those patients with relapse in the lungs only. These results were obtained using alternate courses of cyclophosphamide and etoposide with carboplatin and etoposide; this regimen was 90 weeks long, and most children had discontinued the therapy due to prolonged hematological toxicity. In a previous experience, Malogolowkin et al treated 27 patients with alternating carboplatin/etoposide and ifosfamide/doxorubicin. The 3-year EFS and OS for these patients was 58%.\(^5\)

G. References


H. High-dose Chemotherapy and Autologous Stem Cell Rescue

The role of high-dose chemotherapy and autologous stem cell rescue (ASCR) in patients with high-risk relapsed WT is not fully defined. High-dose chemotherapy with ASCR has been used worldwide but mostly outside controlled clinical trials. Since the first report by the European Bone Marrow Transplant (EBMT) group, the number of WT patients registered in the EBMT registry has grown to more than 300.

Overall, experiences testing high-dose chemotherapy and ASCR seemed to obtain a better outcome than historical controls, with 3- or 4-year OS rates ranging from 60% to 73%. Pein et al reported transplantation in 28 high-risk chemotherapy-responsive patients, and the 3-year OS and DFS were 60% and 50%, respectively. Conditioning chemotherapy consisted of melphalan, etoposide, and carboplatin (MEC) in all the cases. Kremens et al described 23 patients who were treated with high-dose chemotherapy and ASCR (in 18 children, the conditioning course was MEC) after various reinduction regimens; the OS was 60.9%, and the EFS was 48.2%. Campbell et al showed 4-year EFS and OS rates of 60% and 73%, respectively, in 13 patients who underwent single...
or double ASCR after various conditioning regimens. Spreafico et al reported 20 consecutive children with high-risk features at relapse; all the children received an intense-dose chemotherapy induction, and most of them adopted an ICE-based therapy, and 15/20 received high-dose chemotherapy and ASCR as consolidation. This group elected to reduce drug dosage of the ICE and MEC associations vis-à-vis the doses used by others in an attempt to reduce the expected toxicity without jeopardizing the outcome; reduced-ICE consisted of ifosfamide, 1500 mg·m⁻²·d⁻¹ × 4 days; carboplatin, 600 mg·m⁻²·d⁻¹ × 1 day; and etoposide, 100 mg·m⁻²·d⁻¹ × 4 days. The 3-year DFS and OS rates were 56% and 55%, respectively.

The UKCCLG’s strategy for patients with relapsed high-risk disease was based on reinduction dose-intense regimen and a consolidation with high-dose chemotherapy and ASCR. The reinduction chemotherapy alternated carboplatin and etoposide with cyclophosphamide and etoposide. After 6 chemotherapy courses, responding patients received high-dose of a single agent, melphalan, with ASCR.

There are no randomized trials that compare conventional dose chemotherapy to high-dose chemotherapy. However, our North American colleagues reported a series of children who were treated with either conventional or high-dose chemotherapy according to the tumor response to induction chemotherapy. This Children’s Cancer Group study of 66 patients with recurrent high-risk WT used cyclophosphamide (440 mg·m⁻²·d⁻¹ × 5 days) and etoposide (100 mg·m⁻²·d⁻¹ × 5 days) and alternated them with carboplatin (500 mg·m⁻²·d⁻¹ × 2 days) and etoposide (100 mg·m⁻²·d⁻¹ × 3 days) and gave a response rate of 78% (42% complete response and 36% partial response after 2 courses). Patients who achieved complete response received maintenance therapy with further 5 identical pairs of courses, while those with partial response or stable disease received ablative chemotherapy followed by ASCR. The 3-year EFS was 59% and 40%, for the maintenance and ASCR subgroups,
while the 3-year OS was 64% and 42%, respectively. Although the maintenance chemotherapy group showed better outcome than the ASCR group, there was a selection bias such that patients who were disease free after induction therapy received standard-dose chemotherapy, whereas patients with residual disease received ASCR.

In conclusion, the previously mentioned reports were not uniform in their definition of “high-risk” disease (responsive or not responsive to miscellaneous reinduction chemotherapy or those that show different disease status at the time of transplant), and they adopted various conditioning regimens (single or tandem transplant, different agents). Direct comparisons are limited by these differences. While it is not clear which preparative regimen is superior and/or less toxic, it does seem that there is a survival advantage for those patients whose recurrent disease was chemo-sensitive and for those without disease evidence prior to transplant.

Taken together, these studies seem to suggest a role for dose-intensive strategies for treating children with relapsed high-risk WT, although there is no consensus on whether high-dose chemotherapy with ASCR accounts for the improvement in post-relapse outcomes compared to historical published data.

H. References

I. Topotecan

Topotecan, a camptothecin analog that interacts with DNA topoisomerase I, demonstrated antitumor activity in different childhood cancers, including WT.\(^1\) The schedule of administration was probably important in determining its activity, with the protracted schedule being more effective than an intermittent high-dose regimen. Investigators at the St. Jude Children’s Research Hospital studied its activity specifically on WT, both in pre-clinical models and in clinical phase I and II trials.\(^2,3\) In the St. Jude-based WILTOP phase II study, a response rate of 48% was seen in 25 evaluable heavily pretreated favorable histology WT patients (12 partial remissions, 6 stable diseases, and 7 progressions).\(^4\) The encouraging results obtained in the WILTOP study differed from previous topotecan trials.\(^1,3\) and were ascribed to the protracted topotecan schedule (the action of poisons during S phase is optimized by longer exposure).

Based on these experiences, topotecan has been variably included into salvage strategies for high-risk recurrent WT patients in the past few years; however, these strategies have been used only in a limited number of patients at the discretion of the treating physician. Following the results obtained with topotecan, in the current Children’s Oncology Group’s (COG) high-risk renal
tumor study (AREN0321), the response to irinotecan, a potent topoisomerase I inhibitor, in a newly diagnosed stage IV diffuse anaplastic WT is under investigation\(^5\) (Perlman 2005) and might give us some insights in patients with recurrent WT as well.

I. References


J. Very High-risk Relapsed Wilms Tumor

Patients with relapsed diffuse anaplastic tumors have dismal long-term survival rates regardless of the site or the time of relapse.\(^1\)\(^-\)\(^3\) Blastemal-type WT after primary chemotherapy has been identified by SIOP researchers as a poor prognosis group at diagnosis; patients with this WT histology who relapse have a dismal prognosis after recurrence compared to diffuse anaplastic tumors.\(^4\)

Overall, very poor responses to any drug or drug combination have been reported in these 2 groups of patients (i.e., diffuse anaplastic WT and blastemal-type WT after chemotherapy). In the analysis by Pinkerton et al, 1 out of 7 patients with unfavorable histology responded to second-line chemotherapy;\(^5\) in a study conducted by WILTOP, only 2 tumors partially responded to topotecan out of the 11 diffuse anaplastic relapsed WT.\(^6\)
No survivors were registered among the 9 anaplastic WT patients who relapsed in the retrospective analysis survey from St. Jude.\textsuperscript{7}

For some standard-risk or high-risk patients with relapsed WT for whom the cause of initial treatment failure might have been the relative undertreatment they received upfront. We speculate that for some very high-risk children the intrinsic resistance to drugs may be the main cause of treatment failure both at diagnosis and relapse. Because very high-risk patients will already have received the most conventional active agents as part of their initial therapy, the inclusion of these patients onto trials of novel agents is justified.

\section*{J. References}


K. New Agents and Novel Approaches

Since the number of relapsed WT cases is limited, there have been few children with WT who have entered phase I or II studies for relapsed pediatric solid tumors. Apart from isolated case reports on single promising agents, like taxane,\textsuperscript{1,2} the data from controlled clinical trials is very scanty and non-conclusive.

Oxaliplatin has broad antitumor activity, including tumors that are resistant to carboplatin. However, since the available data are from 2 patients enrolled in 2 different phase I pediatric trials (only oxaliplatin\textsuperscript{3} and oxaliplatin/etoposide\textsuperscript{4}) with no documented response, no conclusion can be made about the potential efficacy of this agent for the treatment of recurrent WT.

Antiangiogenic drugs that concentrate on the activity of vascular endothelial growth factor (VEGF) as a potential target\textsuperscript{5} have been investigated. However, what emerged was that the pathways regulating angiogenesis in WT are very complex, and single-drug therapy is likely to be unsuccessful due to the early onset of resistance. Bevacizumab, a monoclonal antibody directed against VEGF, was administered in a phase I study conducted by the Children’s Oncology Group (COG) that included 2 patients with WT. Neither patient showed an objective response. Bevacizumab was also administered to 2 children with WT on a compassionate basis (no information on their histology is available).\textsuperscript{6} Temporary disease stabilization was achieved in both the patients; in the second case, the patient was treated with combination topotecan. Instead of targeting the ligand, some of the newer agents inhibit the VEGF tyrosine kinase signaling receptors, i.e., VEGF receptor-1 and -2. As a group, the tyrosine kinase inhibitors are less specific and may affect signaling at varying degrees through parallel angiogenic pathways, platelet-derived grow factor receptor (PDGFR), and fibroblast growth factor receptor (FGFR). In more recent studies in
adults, antiangiogenic agents have been tested in combination with cytotoxic chemotherapy, with a potential additive or even synergistic effect.

A phase II trial conducted by the COG tested the differentiation effects of all-\textit{trans}-retinoic acid and interferon-\textit{\alpha}2a on 14 evaluable WT patients, and no responses were registered.\textsuperscript{7} Despite this, a recent case report of a patient with a chemotherapy-resistant refractory bilateral nephroblastomatosis by Witt \textit{et al} showed an excellent response to 13-\textit{cis}-retinoic acid in combination with V and A.\textsuperscript{8}

\section*{K. References}


\section*{L. Future Perspectives}

Due to a small number of patients with relapsed WT, advancements in the treatment that will lead to improvement in the outcomes of high-risk patients
and a decrease in the morbidity associated with therapy of standard-risk patients will be feasible only through the development of international cooperation and well-designed clinical trials.

These studies should include biological evaluation of the recurrent tumors that may provide insights into the genetic mechanisms of drug resistance, tumor progression, and relapse. The identification of these molecular events may provide information about new targets for novel therapeutic approaches to be used in future trials for the treatment of these patients.