REAL-WORLD IMPLEMENTATION OF NORTH AMERICAN AND SIOP STRATEGIES FOR THE TREATMENT OF WILMS TUMOR IN URUGUAY

Diana Vargas¹, Luisa Chantada², Bruno Cuturi¹, Anaulina Silveira¹, Ángeles Rodríguez¹, Luján Guerrero¹, Lucia Díaz¹, Mariela Castiglioni¹, Fabiana Morosini¹, Carolina Pagés¹, Elizabeth Simón¹, and Luis Castillo¹

¹Sindicato Medico del Uruguay
²Universidad de Buenos Aires

September 5, 2022

Abstract
We performed an audit from 1995 to 2020 of patients with Wilms tumor in a referral center in Uruguay. Treatment included North American (NA) strategies (n=23) up to 2004 followed by SIOP strategy (n=35) thereafter (stage I-II=28, III=7, IV=14 and V=9). Delay in local radiotherapy was noted (median of 21 days after surgery). There was no toxic or surgical death or abandonment. Five-year pOS was 0.72 and 0.92 for the NA and SIOP respectively. Results favored the SIOP strategy with no unexpected toxicities and high treatment compliance in both strategies. Timely implementation of radiotherapy was challenging.

INTRODUCTION
Wilms tumor (WT) is the most common renal tumor in children and it has been selected by the World Health Organization as an index tumor for priority global action ¹². Despite excellent results were reported from major cooperative groups, survival results in Latin America are partially known³⁴. In Latin America and in most low and middle-income countries (LMIC), the use of the International Society of Pediatric Oncology (SIOP) protocols based on preoperative chemotherapy that allows secondary surgery have been increasingly used³⁴. They led to lower frequency of tumor rupture and a lower use of radiotherapy and anthracyclines but overall survival is comparable to North American-NWTS (NA) strategy which proposes upfront surgery. However, the potential benefit of the SIOP strategy in middle or upper middle-income countries is not clear⁶⁷.

In our center, over the past 25 years, we applied sequentially the NA and the SIOP strategy, allowing for a comparative analysis. Thus, with the aim of evaluating the implementation and results of both strategies, we conducted a retrospective study in which patients diagnosed with nephroblastoma treated at our center between January 1995 and December 2020.

RESULTS
Patients treated from 1995 to 2004 received a NA strategy⁸, while from 2005 onwards the predominant approach was that of the SIOP-2001 and then the Umbrella 2016 protocol⁹, without major modifications with respect to the original protocol. All patients received a thoracoabdominal computed tomography with oral and intravenous administration of contrast for staging and those with diagnosis of lung metastasis on the computed tomography scan were considered stage IV. Sixty consecutive patients were identified (two were excluded, one because incomplete records and one because a change in diagnosis after pre-operative chemotherapy and secondary nephrectomy). Twenty-three patients were treated with the NA strategy and
35 with the SIOP protocols. Median age was 36 months (range 7 to 167) and stage included: I-II=28, III=7, IV=14 and V=9. Results according to treatment strategy are shown in Table 1. Four patients had associated congenital malformations, however no case of syndromes typically associated with WT were detected.

A fine needle aspiration (FNA) was done in 11 patients for diagnosis (4 in NA strategy and 7 in SIOP strategy) Surgery included conventional radical nephrectomy with lymph node sampling in all stage I-IV cases (including thrombectomy in 2 cases) and different instances of nephron sparing surgery in those cases with stage V. Surgery was performed at a median of 10 days (range 2-28) after the end of pre-operative chemotherapy in non-stage V patients treated with the SIOP strategy who underwent pre-operative chemotherapy. There were 3 (5.2%) events of tumor rupture during surgery. Other surgical complications included the development of a urinoma followed by fistula in a child with bilateral WT tumor who underwent partial nephrectomy. A total of 21 patients received radiotherapy including flank (n=12) and abdomen (n=10) (doses 10.2 Gy to 25.5 Gy) and lung (n=6) at 12 Gy. Radiotherapy was delivered by linear accelerator equipment. Median time of delivery of abdominal/flank radiotherapy was 21 days (range 9 to 83) after surgery. On histopathology examination, 5 cases showed diffuse anaplasia (8.6 %). Adjuvant chemotherapy included anthracyclines in 27 cases (52 %).

There was no toxic or surgical death or abandonment. One patient developed grade IV neurological toxicity after vincristine so the drug was discontinued.

Eleven patients (18.9%) relapsed or progressed (6 in the NA group and 5 in the SIOP group) and 7 (12%) of them died of tumor progression (6 in the NA and 1 in the SIOP group). Of the relapsing patients, 3 had stage II, 6 had stage IV and 2 had stage V. Relapse was metastatic (7), local or both (4). All these patients were treated with intention to cure and 4 survive disease-free (all in the SIOP group and two had stage II and two stage V). Three patients received high dose therapy with autologous stem cell rescue for the treatment of relapse (all died). Two of the patients that relapsed had diffuse anaplastic histology but in one of them, it was only detected at second opinion after relapse.

With a median follow-up of 7.5 years (range 1 to 22), 5-year pEFS and pOS were 0.84 (SE 0.05) and pOS 0.87 (SE 0.05) respectively, with a significant difference favoring the SIOP strategy (Table 1).

DISCUSSION

Our study shows that a high survival rate can be achieved at a referral center in Uruguay using either the NA or the SIOP strategies but the later yielded better survival results. This survival difference was mainly justified because of better results in stage IV patients however, there was a trend for a lower number of stage III patients. Adequate oncological and surgical management as well as universal access to chemotherapy and good supportive care were essential for success of both strategies in our setting. However, even though we found that both chemotherapy protocols can be delivered on time with no unanticipated complications and surgery can be performed safely and timely, there were still some deviations for the international recommendations that need to be addressed. Despite having free access to radiotherapy which is available on campus, we found that there was a delay in its administration compared to the international recommendations which did not improve with time. This problem in LMICs is influenced by many factors such as delay in the scheduling of the patients usually because high demand, delay in the pathology report necessary for the indication of radiotherapy, possibly higher rates of surgical complications and wound healing making it not possible to administer radiotherapy on time. Nevertheless, our local-regional relapse rates are in the range of the international literature, albeit in a small population. Another deviation from the international studies was a slightly higher use of FNA.

Anthracyclines were needed in 46.5% of the cases with no major differences between strategies, which is slightly higher than the figures from high income countries, but justified by the relatively higher number of advanced cases in our series. Like other series from our region, a higher proportion of patients with metastatic disease was found (24.1% in our study compared to 11% to 17% in the contemporary international studies) which may reflect late diagnosis and also referral patterns since an additional 20% of patients with WT in our country are treated at private institutions and higher risk cases are more likely to be referred.
to our hospital. Therefore, this difference in stage distribution, including a higher proportion of advanced cases, should be considered when evaluating comparative survival results or overall relapse rates in the whole population. Also, a relatively high number of patients with stage V tumors was also probably related to referral patterns.

Lastly, the fact that ours is a national referral center in a small country with egalitarian access to care provides a favorable environment to accurately assess real-life outcomes like this study but this may not be possible in other settings, which may be of potential interest for international implementation plans.

To conclude, most patients with WT survived and the SIOP strategy was associated to improved results. Scheduling radiotherapy as recommended by both strategies was not realistic in our setting and we found a delay of its administration.

REFERENCES

Hosted file