CASE REPORT

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Medulloblastoma treatment in a child on dialysis

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Practice Points

- Managing patients who suffer from both cancer and end-stage renal disease is challenging, especially in children.
- The experience of chemotherapy in children undergoing hemodialysis is limited.
- We describe the case of a 5-year-old child on chronic hemodialysis who developed a medulloblastoma that was successfully treated with a cyclophosphamide- and vincristine-based regimen after surgery and craniospinal irradiation.
- Given the impaired renal function, it is important to avoid improper use of chemotherapy in dialyzed children because it can lead either to an oncologically inadequate treatment or potentially fatal toxic effects.

SUMMARY Managing patients who suffer from both cancer and end-stage renal disease is challenging because there is a paucity of data, especially for children. There are no published reports of adjuvant chemotherapy for medulloblastoma being used in children on dialysis. In this article we describe the case of an Italian 5-year-old boy on hemodialysis for chronic renal failure who presented with a desmoplastic medulloblastoma with extensive nodularity and nuclear β -catenin expression. The patient was treated with craniospinal irradiation after complete surgical resection, followed by six cycles of cyclophosphamide and vincristine. Vincristine was administered at the usual dosage for children with normal kidney function, cyclophosphamide was delivered after dialysis and over the course of the following day, starting with 50% of the commonly used dosage. This is the first case report of chemotherapy given during hemodialysis in a child with medulloblastoma. This treatment proved easy to administer despite the child's kidney disease and it maintained disease remission with no additional toxicity.

Medulloblastoma is the most common malignant brain tumor in children. Current treatment protocols include surgery, craniospinal irradiation and platinum-containing chemotherapy [1]. Adjuvant chemotherapy for medulloblastoma in patients on hemodialysis has not been described

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in the literature and little is known about the doses used in children with renal failure [2]. When oncologists are faced with patients who suffer from both cancer and end-stage renal disease, their management is challenging – especially for pediatric patients – because it is hard to find information about the optimal timing of treatment and the dosage adjustments needed to fit in with the patient's dialysis sessions. A shortage of knowledge and data on the use of chemotherapy in renal insufficiency may lead to its improper use, leading either to an oncologically inadequate treatment or potentially fatal toxic effects. Given the impaired renal function in these patients, reduced doses of anticancer drugs that are excreted through the kidneys are often recommended to avoid adverse drug reactions, and it becomes important to know how hemodialysis can affect the clearance of certain anticancer drugs to adjust the timing and the dosage of administration [3].

We describe the case of a 5-year-old child on chronic hemodialysis who developed a medulloblastoma that was successfully treated with a cyclophosphamide- and vincristine-based regimen after surgery, and craniospinal irradiation.

Case report

A 5-year-old boy with congenital anomalies of the kidneys and urinary tract had chronic renal failure and had been on peritoneal dialysis from the age of 6 months. During the period on peritoneal dialysis he underwent two renal transplants, which immediately failed due to thromboembolism. At the age of 5 years, the patient was switched to hemodialysis three times a week because of recurrent peritonitis.

Soon after the beginning of hemodialysis, the boy started to complain of intradialytic fatigue and headache, associated with vomiting. For 1 month, a dialysis disequilibrium syndrome was suspected [4], then computed tomography revealed an expansive lesion in the posterior cranial fossa. MRI of the brain and spine confirmed the posterior fossa lesion, with no other sites affected. Radical surgical resection of the mass was performed and the final pathological diagnosis was desmoplastic medulloblastoma with extensive nodularity and 5% nuclear β -catenin expression (Figure 1). Staging after surgery excluded any local residual or cerebrospinal fluid involvement. Adjuvant treatment should have included craniospinal radiotherapy,

with a boost to the tumor bed, followed by eight courses of chemotherapy (vincristine, lomustine and cisplatin) [5].

The kidney disease is not part of a syndrome and the medulloblastoma is not related to this pre-existing condition. At the time of medulloblastoma diagnosis, karyotype assessment was normal. Given the child's renal disease, cisplatin's toxicity and pharmacokinetics (kidney excretion and removal by dialysis), the unpredictable hematological toxicity of lomustine in this setting and the patient's favorable prognostic factors (complete excision, no metastases and nuclear β -catenin expression) [6], a multidisciplinary institutional and extrainstitutional case discussion led to the patient being scheduled to receive the least toxic, but still effective treatment that we could conceive. After radiotherapy (craniospinal irradiation: 23.4 Gy plus 30.6-Gy boost to the posterior fossa; standard daily fractionation of 1.8 Gy), the boy was treated with vincristine at the same dose used in children with normal renal function (day 1 bolus of 1.4 mg/m²) and cyclophosphamide, starting with 500 mg/m²/day for 2 successive days, administered as an intravenous 1-h infusion upon dilution with 150 ml/m² of saline, increasing the dosage, after assessing its tolerability, to up to 1250 mg/m² (total dose) from the second cycle onwards, for a total duration of six courses. Vincristine was administered at the end of the hemodialysis session; cyclophosphamide was delivered after dialysis and over the course of the following day (24 h before the following session). Growth factors (filgrastim) were used to prevent infectious disease, and reduce the duration of neutropenia and the incidence of febrile neutropenia by the mobilization of peripheral blood progenitor cells. The usual therapy of the child (phosphate binders, vitamin D, ferrum and recombinant human epoetin) was continued. At the time of writing, 35 months after diagnosis, the patient is undergoing routine neurological and endocrinological follow-up and is continuing to have hemodialytic treatment three times a week. Follow-up tests revealed hormonal alterations, including increased levels of prolactin, parathyroid hormone and ACTH, which are possible endocrinological complications in patients on dialysis. The thyroid function remains normal and the value of IGF1 is within normal limits. No neurocognitive impairment of the child was evident when assessed with the following neurocognitive assessments: wechsler scales (according to age); full IQ; verbal IQ; and performance IQ.

Figure 1. Desmoplastic medulloblastoma with extensive nodularity and 5% nuclear β -catenin expression. (A) The tumor has a lobular architecture and is composed of pale nodular areas with small round neurocytic cells. The internodular component is markedly reduced. **(B)** Immunostain for β -catenin protein shows nuclear positivity in 5% of neoplastic cells. **(C)** The nodules are surrounded by dense collagen tissue.

Discussion

Medulloblastoma and other neuroectodermal tumors account for 16–25% of all cases of CNS tumors in childhood [7]. Current treatment protocols, which include surgery, craniospinal irradiation and chemotherapy, have achieved 5-year overall survival rates of over 70% for standard-risk patients [5,8].

After maximal safe surgical resection, the gold standard for patients over 3 years of age at diagnosis, with no residual tumor or metastases, is craniospinal irradiation with a total dose of

23.4 Gy plus a boost to the posterior fossa or tumor bed of up to a total dose of 54 Gy. This is usually combined with a concurrent weekly single-drug (vincristine) and, subsequently, multidrug regimen, alternating between cisplatin, vincristine and lomustine, or cisplatin, vincristine and cyclophosphamide regardless of histology [9,10].

Patients with end-stage kidney disease secondary to conditions such as diabetes, nephroangiosclerosis, polycystic kidney disease, urinary tract disorders and glomerular diseases have benefited

from substantial improvements in renal replacement therapies in the last decades, and now have a substantially longer life expectancy [11].

In children on dialysis who develop cancer, it is important to balance the benefits of life-saving chemotherapeutic drugs against the risks of serious adverse effects. Only a few data are available on cancer treatment in dialyzed children, which makes the choice of treatment in these cases far from standardized. It is obviously essential to reduce the dosage of cytotoxic drugs if they are excreted through the kidneys, but no studies have described the pharmacokinetics and clearance of these drugs during dialysis to enable the timing and dosing of their administration to be optimized.

Among the standard chemotherapeutic drugs available, vincristine is not excreted through the kidneys and cannot be eliminated by dialysis, so it has been used in patients with renal disease without changing the dosage compared with that used in patients with a normal kidney function. Cisplatin is mainly eliminated through the kidney and its dose should consequently be reduced in patients with end-stage renal disease; free cisplatin is dialyzable and cisplatin removal during hemodialysis should, therefore, be taken into account. Even if nephrotoxicity is no longer a major limitation in hemodialysis patients, the risks of potential dose-related side effects must be considered, such as ototoxicity, anemia and neuropathy. Although good results have been reported with the use of cisplatin in adults on dialysis, to the best of our knowledge, only one case report has been published concerning the use of this drug in a child with hepatoblastoma on peritoneal dialysis: after assessing its pharmacokinetic properties, a dose equating to 25% of the standard dosage was administered [2]. Given the lack of data specific to children on hemodialysis, the abovementioned pharmacokinetic profile and the availability of some alternatives, we did not consider cisplatin as the ideal drug for our patient and preferred not to use it. Lomustine markedly reduces blood cell counts, so we chose not to use it in order to avoid any hematological and infectious toxicity, which could have interfered with the whole treatment program. Regarding cyclophosphamide, 30–60% of the total cyclophosphamide dose is eliminated through the kidneys as cyclophosphamide or metabolites, and a dose reduction of 25% has been suggested for patients on hemodialysis; more importantly, cyclophosphamide is removed

by hemodialysis and, therefore, the drug should be administered after the dialysis session.

Taking into account all the abovementioned issues, cyclophosphamide and vincristine were used. The choice of the drugs was debated in multidisciplinary meetings with oncologists, nephrologists and other European experts in the field of pediatric oncology. The decision taken to treat the patient with vincristine and cyclophosphamide following surgery and radiation therapy was based on the rationale of minimizing toxicity, since radiation therapy can be efficacious for desmoplastic medulloblastoma with extensive nodularity. Vincristine was used at the same dosage suggested for children with normal kidney function (1.4 mg/m²), while cyclophosphamide was administered according to a schedule based on its possible and proven tolerability, starting with 50% of the commonly used dosage and increasing the doses by 25% from the second course up to the end of the treatment. Since cyclophosphamide is removed by hemodialysis, it was administered after the session and in the interdialytic day. This schedule was well tolerated and effective in maintaining disease remission. Predialysis urea and creatinine did not change significantly during and after chemotherapy (urea: 160 vs 128 mg/dl; and creatinine: 8.23 vs 6.83 mg/dl) as well as urine output. However, it is important to emphasize that, for patients on hemodialysis, nephrotoxicity is not a crucial issue.

McCune JS *et al.* reported the pharmacokinetic disposition of cyclophosphamide and of its two metabolites in an anephric child with bilateral Wilms tumor [12], but additional pharmacokinetic and pharmacodynamic data are warranted in future studies to provide more accurate dosage recommendations. In fact, there are few data on chemotherapeutic drug pharmacokinetics in children with reduced kidney function or during dialysis. The dosage adjustment and time of administration regarding the dialysis session need to be further investigated to optimize cytotoxic drug therapy and to minimize toxic effects in those patients, and to provide preliminary recommendations for chemotherapy in children on dialysis.

The boy remains disease free 35 months after his medulloblastoma was diagnosed. He is currently undergoing routine neurological and endocrinological follow-up, and continuing with his hemodialytic treatment three times a week. His complex endocrinological situation

warrants a close endocrinological assessment to identify any sequelae of radiotherapy and kidney disease [13].

Conclusion

This is the first case report of chemotherapy given during hemodialysis in a child with medulloblastoma. The experience of chemotherapy in children undergoing hemodialysis is limited. Only a few cases have been reported in the literature. In this case, the treatment proved easy to administer despite the child's renal disease and it maintained disease remission with no toxicity. The successful treatment of this patient was naturally also thanks to his favorable tumor-related prognostic factors (complete excision, no metastases and nuclear β -catenin expression). Based on the low level of β -catenin expression, we cannot consider this case of medulloblastoma to belong to the WNT subgroup of molecular classification [14]. However, from our point of view, it is important to emphasize the presence of nuclear β -catenin also in light of the subsequent clinical history. The lack of pharmacokinetic data is clearly the major limit of our report, but unfortunately we were unable to perform this kind of analysis. However, the good clinical response and the absence of significant side effects could probably be viewed as an indirect sign of adequate drug dosage. Even taking into account this important limitation, sharing our experience could be useful in clinical practice, given the complexity of patients who suffer from both cancer and end-stage renal disease, the paucity of pediatric data available on the use of chemotherapy in children on hemodialysis, the impossibility of designing large studies on this issue, and the

dramatic events possibly associated with under- or over-dosage of chemotherapy in this peculiar population.

Future perspective

Impressive steps have been made in the last 5 years in the field of molecular mechanisms that now allow us to divide medulloblastoma into four distinct subgroups. More progress, after exploring genomics and transcriptomics, will occur through exploration of other regulatory levels such as epigenetics. The identification of other molecular targets after SMO in the SHH pathway will allow the introduction of targeted treatments that are hopefully less toxic for any child.

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Informed consent disclosure

The authors state that they have obtained verbal and written informed consent from the patient/patients for the inclusion of their medical and treatment history within this case report.

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