Hyperthermic intraperitoneal chemotherapy (HIPEC) as another treatment modality for desmoplastic round cell tumour patients: first paediatric experience from UK

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SUMMARY

We present the first young paediatric patient with desmoplastic small round cell tumour (DSRCT) treated in UK with hyperthermic intraperitoneal chemotherapy (HIPEC). A 7-year-old girl was diagnosed with abdominal DSRCT with peritoneal and liver metastases. After six cycles of chemotherapy she obtained a partial response, including almost complete resolution of the two liver metastases. It was decided to pursue cytoreductive surgery (CRS) combined with HIPEC, a procedure commonly performed in adults, but seldom in a child. The surgery was macroscopically complete and the HIPEC uncomplicated. She continued treatment without delays, including whole abdomino-pelvic radiotherapy and maintenance chemotherapy (cyclophosphamide/vinorelbine for 12 months). She is currently in complete remission 4 months after end of treatment and 26 months after diagnosis. HIPEC was made possible by successful collaboration between multiple teams. CRS-HIPEC proved to be safe and feasible and could be offered to other children with diagnoses of peritoneal malignancies across the UK.

BACKGROUND

Desmoplastic small round cell tumour (DSRCT) is a highly aggressive, rare sarcoma, typical of men in their third decade of life.[1] The most common presentation is a large abdominal mass, with metastases to abdominal organs, in particular liver and omentum, and more rarely to lungs and other distant organs.[2] DSRCT is characterised by a chromosomal translocation t(11;22)(p13;q12) resulting in the fusion of Ewing's sarcoma (EWS) and the Wilms' tumour suppressor gene (WT1).[3]

Despite multimodal intensive treatment including chemotherapy, whole abdomino-pelvic radiotherapy (WAP-RT) and cytoreductive surgery (CRS), the 5-year overal survival (OS) is 5% to 20%.[4 5] New agents including pazopanib, trabectedin and ramucirumab are being tried in clinical practice in the hope of improving outcomes.[6 7] Both the achievement of macroscopically complete resection (defined as complete or nearly complete cytoreduction)[8] and delivery of radiotherapy correlate with probability of survival, thus highlighting the role of local control in the treatment of this malignancy.[2]

Hyperthermic intraperitoneal chemotherapy (HIPEC) is routinely used in adults for the treatment of *pseudomyxoma peritonei*, but its role in DSRCT remains to be determined. A recent analysis of outcome in 100 patients treated in France reported a 5-year OS of 5%.[5] Factors that correlated to survival were female gender, receiving WAP-RT, MD Anderson stage I disease (no metastatic spread or nodal involvement) and complete macroscopic resection. Fifteen patients also received HIPEC: these patients had no extra-peritoneal metastases and complete macroscopic resection was achieved. Among these 15 patients there were no survivors after 5 years. Another large European series[8] could not show evidence of benefit from HIPEC, as only 5 among 60 patients had received it and therefore the report was underpowered to make such a distinction. A phase 2 trial investigating the benefit of HIPEC in sarcomas showed that patients with DSRCT had significantly longer survival compared with other tumours including rhabdomyosarcoma and EWS (median relapse-free survival after surgery 44.3 months vs 12.5 months). Moreover, patients with DSRCT without portal, liver or other metastatic disease had a significant longer recurrence-free survival compared with those with disease at those sites (37.9 vs 14.9 months).[9]

Due to the rarity of DSRCT no randomised trials have been done to investigate the efficacy of HIPEC, but the safety of the procedure has been demonstrated.[10] Hayes-Jordan published the first phase I study in a paediatric population, including 23 patients aged 3 to 21, who underwent 27 procedures.[10] There were no intraoperative or perioperative deaths and no patient required haemodynamic support intraoperatively. Grade 3 or above renal toxicity was found in 5 of 27 patients. There were seven wound infections (three superficial wound dehiscence requiring wound vacuum therapy and four superficial infections requiring antibiotics). Two postoperative small bowel obstructions occurred, one requiring operative intervention. One patient developed a subclinical decrease in hearing and there were two grade 3 haematological toxicities, two grade 3 hepatic toxicities and one grade 3 cardiotoxicity. Twenty-six per cent of patients had a continuous remission 1 to 4 years post the procedure. No details were given on their histologies.

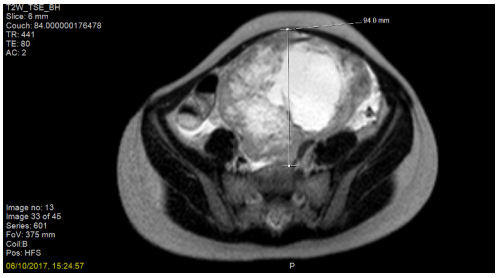

Figure 1 MRI at presentation.

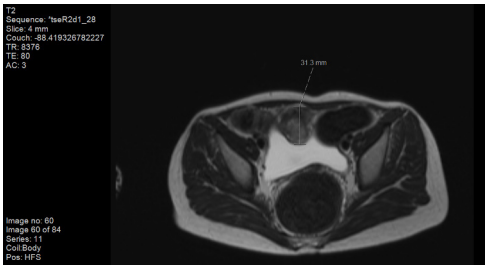

Figure 3 Eight months since diagnosis, prior to surgery and hyperthermic intraperitoneal chemotherapy.

In France, 22 patients aged 4 to 17 underwent HIPEC between 1991 and 2015;[11 12] 7 of which had DSRCT. Fourteen (64%) patients had complications within 30 days from HIPEC, requiring an urgent laparotomy in eight (36%) cases (three haemoperitoneum, three digestive fistulas, one urinary fistula, one bilious peritonitis) and an aponeurectomy for a compartment syndrome in the calf muscle in one case. Three patients needed drainage of a pleural effusion (grade 3). Other complications were one case of septic ascites (grade 3), one case of urinary tract infection (grade 3), one case of thrombocytopenia <50 000 per mm^3, one case of medullary aplasia (grade 2), one case of severe anorexia (grade 3) and one case of pulmonary embolism (grade 4). One patient with DSRCT was alive and disease-free 22 months after the procedure.

In face of the dismal prognosis of DSRCT, these survival data are encouraging although HIPEC carries risk of significant morbidity.

Here we describe the first paediatric case to receive this treatment in UK, after multidisciplinary collaboration between adult peritoneal malignancy services, paediatric oncology and surgery and intensive care services across two hospitals.

CASE PRESENTATION AND MANAGEMENT

A 7-year-old girl presented to our centre with 4 to 6 weeks history of constipation and mild abdominal distension, and was found to have a large pelvic mass, (figure 1) peritoneal metastases and two small liver metastases. A biopsy gave the diagnosis of DSRCT, with EWS/WT1 translocation, MD Anderson stage III. Chemotherapy was started using a compressed schedule of vincristine/doxorubicin/cyclophosphamide alternated to ifosfamide/etoposide (ie,) every 2 weeks, with intensive supportive care.[13] After 6 courses of chemotherapy she achieved a partial response, with almost complete resolution of the liver metastases, and reduction in the size and metabolic activity of the main pelvic mass and of the peritoneal nodules as seen in figure 2 and pre-surgery in figure 3. The decision was made to attempt surgical resection (including peritonectomy) with HIPEC. As the liver metastases were resolving and hardly detectable at routine radiological investigations, a decision was made to monitor these rather than resect them at the time of peritonectomy. The team at the Peritoneal Malignancy Institute Basingstoke was contacted and given that its expertise does not extend to the paediatric age, collaboration between this team and the paediatric surgical team at the specialist paediatric oncology centre of the patient was established.

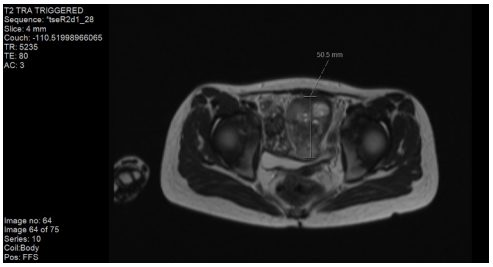

Figure 2 Five months since diagnosis: partial response.

The preparation for the surgery required 3 months of close collaboration between the adult peritoneal malignancies surgical team and the paediatric surgical team. Two surgeons, two nurses and an anesthesist from the peritoneal malignancy unit were granted honorary contracts at the specialist paediatric oncology centre. Members of the paediatric teams (including a paediatric surgeon, anaesthestic/intensive care consultant and theatre nurses) visited the Peritoneal Malignancy Institute and observed the HIPEC procedure being performed in adult patients. The manufacturer of the HIPEC chemotherapy equipment (Gamida) provided a HIPEC SunChip 2 chemotherapy machine on compassionate grounds.

Standard operating procedures from the peritoneal malignancy unit were adapted to produce paediatric policies and procedures for chemotherapy prescribing, dispensing, delivery to theatre and waste disposal. The procedure was approved by the Drug and Therapeutics Committee at the patient's specialist paediatric oncology centre and by the medical directors of the involved hospitals. Expert advice was sought on paediatric drug doses and practice and pharmacy was involved in the preparation of the chemotherapy. The family was asked to consent both to the surgery and HIPEC procedure, and understood that this was the first CRS and HIPEC procedure on a child under 12 in UK.

The child underwent complete macroscopic resection of the pelvic mass along with peritonectomy and omentectomy with HIPEC. Cisplatin 100 mg/m^2 was left for 90 min at a temperature of 41°C in the peritoneal cavity prior to closing the surgical site. The surgery and HIPEC was well tolerated with no complications, and the child was discharged from paediatric intensive care on postoperative day 7 and discharged home on postoperative day 11. The pathology confirmed the diagnosis of DSRCT, with 60% of viable tumour. Nodules were found with viable tumour from diaphragm, left fallopian tube and ovary and from small bowel.

OUTCOME AND FOLLOW-UP

The patient started WAP-RT (36 Gy) 6 weeks after surgery. She then received maintenance chemotherapy with vinorelbine/cyclophosphamide (cyclophosphamide 25 mg/m^2 per day by mouth, vinorelbine 25 mg/m2 per day intravenous on day 1, 8 and 15 of each cycle) for 12 months. Since completing treatment, surveillance with chest X-ray every 3 months and MRI of abdomen and pelvis every 3 months has demonstrated continued

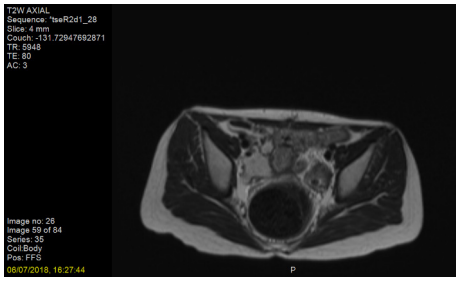

Figure 4 Thirty days post surgery and hyperthermic intraperitoneal chemotherapy. Complete remission.

complete remission 18 months after the surgery, or 26 months after diagnosis. She has improved progressively from a clinical standpoint and she is now attending school on a regular basis. For a representative image post surgery and HIPEC that shows complete remission please see figure 4. For an overview of timeline of the treatment, please see figure 5.

DISCUSSION

The role of HIPEC in children with DSRCT remains controversial.

The initial phase I study[10] and the phase II trial[9] showed prolonged recurrence-free survival in DSRCT compared with other patients with sarcoma. Other publications,[5 8] however have not confirmed these findings. Limitations to all trials are that there is no standardised way of administering HIPEC with inter-study variations in choice of chemotherapy drug, doses, length of treatment and no uniform criteria to select patients. The other limitation in the current evidence is with regard to benefit and safety for children less than 12 years, for which this case report provides data.

Most groups have performed HIPEC in patients with no extraperitoneal disease (MD Anderson stage 1 to 3).[10] Our case met this criterion, as she presented with only two small liver metastases, and had an excellent response to induction chemotherapy. The criteria to consider a patient for HIPEC remain to be defined, as well as the role of HIPEC in patients with extra-abdominal metastases remains to be proven. Further benefit to the patient comes from the surgical expertise that the HIPEC surgeons bring in achieving complete macroscopic clearance, which complements the paediatric oncology surgical expertise.

In our case, several variables have been chosen empirically based on expert advice, rather than evidence. Cisplatin was chosen as chemotherapy agent because the patient had not been exposed to it before and there is literature data supporting its efficacy in HIPEC.[9] Doxorubicin was not considered as our patient had a reduced cardiac function secondary to previous exposure to anthracyclines. The dose of the drug itself, the temperature and duration of intraperitoneal perfusion were based on literature review and expert advice. Randomised trials are not feasible in the paediatric population to identify the survival advantage of HIPEC and optimise the parameters (including drug, dose, temperature and time of exposure) owing to small patient numbers. More research is needed to optimise a procedure, which could improve outcome for patients with an extremely severe prognosis and distinguish between the effect of surgery itself and the addition of HIPEC. A recent multicentre randomised trial in ovarian cancer showed a median survival benefit of 18 months by the addition of cisplatin HIPEC to surgery.[14] This is contrasted by a recent multicentre trial in colorectal peritoneal metastases were there was no benefit to oxaliplatin HIPEC but satisfactory survival from the CRS in both groups.[15] The study highlighted the need for further optimisation of HIPEC, which has the potential to improve outcome in this group of poor prognosis patients.

Our patient had an uncomplicated course but it is important to remember that serious side effects are reported in up to 36% of cases and this remains a high-risk strategy. Accurate long-term follow-up will be needed to identify long-term sequelae to determine what complications are due to the extensive surgery itself or the HIPEC.[16] In the PRODIGE 7 study in colorectal malignancies the 60-day morbidity was significantly higher in HIPEC compared with non-HIPEC group.[15] However, it remains to be seen if this is the case in patients with DSRCT.

This is the first case of CRS and HIPEC in a paediatric centre in the UK. It was only possible through the exemplary collaboration between the national centre at the Peritoneal Malignancy Institute Basingstoke and a specialist paediatric oncology centre for paediatric oncology. In addition, support from the Trust's management, as well as manufacturer of the HIPEC machine, was vital.

Although the long-term survival advantage of this technique is still uncertain, due to the extremely poor prognosis from DSRCT, it may be appropriate to offer this therapy to selected children in the UK.

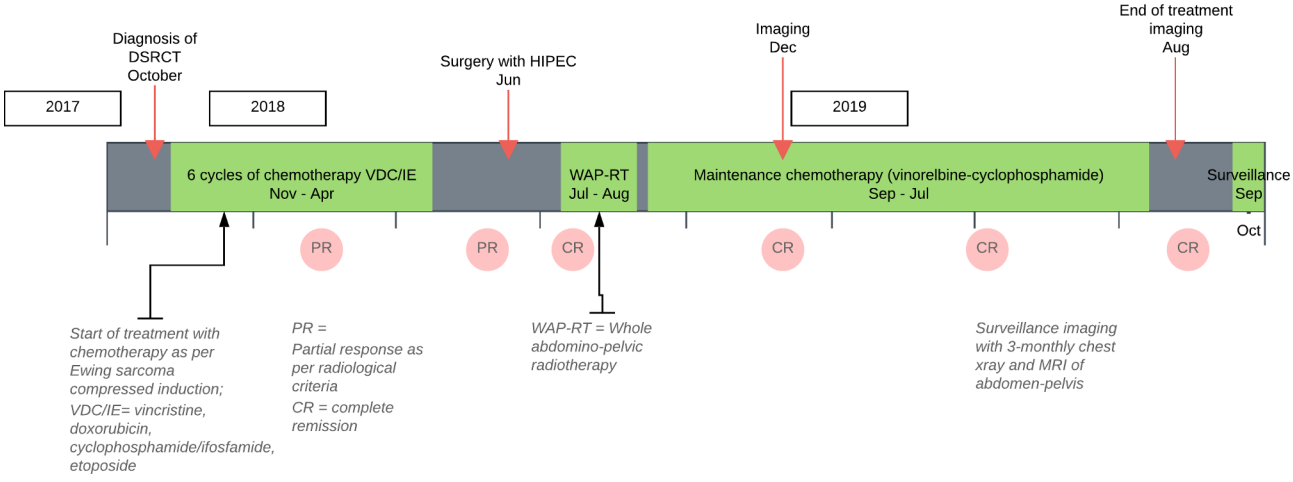

Figure 5 Flow sheet of received treatment. DSRCT, desmoplasticsmallroundcelltumour;HIPEC, hyperthermic intraperitoneal chemotherapy.

Other rare paediatric diseases such as some cases rhabdomyosarcoma, other soft-tissue sarcoma and germ cell tumours in which local control of disseminated intra-abdominal malignancy is very challenging, may also benefit from CRS with HIPEC. However, further data are needed to prove its clinical benefit in these instances.

Patient's perspective

Our family is extremely grateful for all the efforts made so that our daughter could receive the best possible treatment for her disease.

Learning points

- The survival benefit of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) in desmoplastic smallroundcelltumour remains uncertain but HIPEC may play a role in selected patients.
- We demonstrated that collaborative cross-boundary working between teams from different organisations facilitated successful delivery of cytoreductive surgery and HIPEC in a paediatric oncology surgical setting.
- Improved surgical and/or systemic therapies are required for the management of disseminated intraperitoneal malignancy.

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Contributors TSB drafted the case report, reviewed the literature underlying the manuscript and has approved the manuscript's final version. PA devised the case report, reviewed and wrote the manuscript and has approved the manuscript's final version. PA was the primary responsible clinician for the patient that is described in the case report. BO was instrumental in the novel treatment of the patient and developed the manuscript along with the co-authors, and has provided significant input to the manuscript. BO has approved the final version of the manuscript. JCC reviewed the manuscript and contributed significantly to the writing of the manuscript. She also participated in the patient's care as one of the key oncologist. JCC has approved the final version of the manuscript. SD and TC reviewed the manuscript and contributed significantly to the writing of the manuscript. SD also participated in the patient's care as one of the experts of the novel treatment described in the case report. They both have approved the final version of the manuscript.

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