CASE REPORT

Whole abdominopelvic radiotherapy in desmoplastic small round cell tumour of abdomen: a challenge for radiation oncologists

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SUMMARY

An adolescent patient diagnosed with disseminated abdominal desmoplastic small round cell tumour (DSRCT) was taken up for systemic chemotherapy, debulking surgery, stem cell transplant followed by whole abdominopelvic radiotherapy using intensity-modulated radiotherapy. Following this, the patient developed multiple episodes of small bowel obstruction, a known complication of abdominal surgery and radiotherapy. The patient expired due to the complications of bowel obstruction 13 months after the completion of radiotherapy. Though we managed to achieve a complete response at the disease sites with an aggressive therapeutic approach, the patient eventually succumbed to treatment-induced morbidity. Large prospective trials to define management guidelines taking into account quality of life issues may not be feasible for a rare and aggressive scenario such as DSRCT. Therefore, case reports and series reporting not just the treatment techniques and survival, but also the resultant toxicities, will make us vigilant when choosing the intensity of its treatment.

BACKGROUND

Desmoplastic small round cell tumour (DSRCT) is known to be a rare malignancy with a relentless course towards dissemination and low survival rates despite multimodal approach. Its management has remained a dilemma in the paucity of any definite guidelines. Known to be a radiosensitive tumour, whole abdominopelvic radiotherapy (WAP-RT) has been integrated in the treatment algorithm to maximise chances of local control.

Here we are presenting a case of extensive DSRCT in an adolescent treated with chemotherapy, surgery and WAP-RT who remained disease free but with a poor quality of life and succumbed to treatment-induced toxicity.

We, therefore, stress the need to optimise the extent and intensity of surgery and radiotherapy, respectively, with judicious incorporation of newer upcoming modalities to provide a durable local control.

CASE PRESENTATION

A young male patient presented to this institute with decreased appetite, lower chest pain on both sides and progressive distension of abdomen of 1-month duration. An ultrasound of the abdomen

performed at his native place had revealed multiple peritoneal and omental hypoechoic nodules with few peripancreatic, retroperitoneal and multiple mesenteric lymph nodes along with mild ascites with a horseshoe kidney. The patient was brought to this institute for further management.

At presentation, examination revealed a moderately built and moderately nourished patient with a body mass index of 16.89 kg/m² with pallor and a tender, distended abdomen.

INVESTIGATIONS

Contrast-enhanced CT (CECT) of the chest and abdomen revealed multiple nodular deposits in the omentum, mesentery, peritoneal cavity, perihepatic regions with retroperitoneal lymphadenopathy, omental caking and ascites and a horseshoe kidney. Fine needle aspiration and biopsy from the omental mass was reported as malignant round cell tumour. Immunohistochemistry (IHC) showed diffuse positivity of tumour cells for Cytokeratin (CK), focal expression of synaptophysin and desmin and negative for WT-1 and Leucocyte common antigen (LCA), suggestive of DSRCT. Bone marrow aspiration and biopsy did not show any evidence of infiltration by malignant cells.

TREATMENT

Chemotherapy

He was started on neoadjuvant chemotherapy with P6 regimen,¹ along with prophylaxis against *Pneumocystis carinii* as follows:

Cycles 1, 2, 3 and 6 High dose cyclophosphamide, adriamycin, vincristine (HD-CAV)
Cyclophosphamide: 2100 mg/m²/day 6-hour infusion, days 1 and 2 with mesna.

Doxorubicin: 25 mg/m²/day 24-hour infusion, days 1–3.

Vincristine: 0.67 mg/m²/day 24-hour infusion, days 1–3.

Cycles 4, 5 and 7

Ifosfamide: 1.8 g/m²/day 1-hour infusion, days 1–5 with mesna.

Etoposide: 100 mg/m²/day 1-hour infusion, days 1–5.

After the fifth cycle of chemotherapy, a CECT abdomen showed good partial response to therapy with residual nodules and lymph nodes.

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Surgery

An exploratory laparotomy and excision of residual tumour masses were performed. Peroperatively, he was found to have a 2.5×3 cm mass in the rectovesical pouch adherent to the posterior wall of the bladder, multiple peritoneal deposits mainly on the sigmoid colon and parietal abdominal wall, multiple deposits in the omentum adherent to greater curvature of stomach and transverse colon and deposits were seen in the splenic hilum and periportal region. Gross total resection of the tumour nodules and involved nodes was done. Postoperative histopathology revealed residual tumour in the rectovesical pouch, omentum, deposits on sigmoid colon, para-aortic, periportal, peritoneum and appendix; tumour cells were surrounded by desmoplastic stroma.

Adjuvant chemotherapy and stem cell transplant

Two more cycles of adjuvant chemotherapy were administered with the same regimen following which he underwent autologous stem cell transplant. He was then planned for adjuvant radiotherapy.

Radiotherapy simulation

The patient was positioned supine with both hands comfortably placed above head on an all-in-one base plate and immobilised using a four-clip thermoplastic cast. Reference isocentre was placed at mid-abdomen and mid-separation with the help of in-room lasers. About 40 mL of non-ionic contrast was injected intravenously, and simulation CT scan was obtained from mid-thorax to mid-femur with 4 mm slice thickness. These images were transferred to the treatment planning system for CT-based treatment planning.

Target delineation

Contouring of target volumes and organs at risk was done on Eclipse V.11. Information from baseline CECT abdomen, peroperative findings and postoperative histopathology was used for target volume delineation. Target volume included the entire peritoneal cavity, extending cranially from the domes of the diaphragm to the pelvic cavity (figure 1); laterally until the lateral abdominal wall. A 3 mm strip of the surface of liver, spleen, horseshoe kidney, urinary bladder and rectum was included in the target volume as superficial tumour deposits were found peroperatively on these structures.

Planning

Intensity-modulated radiotherapy (IMRT) plan was generated using the Anisotropic analytical algorithm (AAA) algorithm on Eclipse planning system V.11. Two treatment isocentres were placed, one in the upper abdomen and the other in the lower abdomen. Nine coplanar beams were used for the upper abdomen, and seven coplanar beams were used for the lower abdomen plan. Sum of the two plans was generated to evaluate the dose achieved to the target volume and the organs at risk.

Plan evaluation

The dose prescription, dose constraints to the organs at risk and doses achieved were as shown in table 1.

Radiation delivery

IMRT was delivered 5 days a week with daily image verification using on-board imaging. He tolerated the treatment well without any interruptions. Grade 1 nausea and vomiting were well controlled with oral antiemetics and antacids. The patient

Figure 1 Planning target volume including the peritoneal cavity and a strip of the liver and kidney surface in coronal view.

did not report any lower gastrointestinal or urinary symptoms. No haematological toxicity developed during the radiotherapy.

OUTCOME AND FOLLOW-UP

Whole body positron emission tomography CT performed 6 weeks after the completion of radiotherapy showed marked regression in omental and peritoneal deposits and retroperitoneal lymphadenopathy which was metabolically inactive.

The patient developed recurrent episodes of vomiting and abdominal distension at 5 months of follow-up. X-ray abdomen and chest revealed prominent small and large bowel loops and multiple air–fluid levels suggestive of small bowel obstruction. After conservative management, he was taken up for exploratory laparotomy, and adhesiolysis was done with separation of bowel loops from the anterior abdominal wall. Postoperative histopathology did not reveal any tumour cells.

On his last follow-up in this institute, 7 months after completion of radiotherapy, he did not report any vomiting, constipation or abdominal discomfort after oral feeds. Examination revealed a soft abdomen with no palpable mass, organomegaly or free fluid. X-ray of abdomen did not show any abnormality.

However, the patient again developed symptoms of nausea, vomiting and abdominal distension at 13 months but could not be brought to this institute due to financial constraints. Evaluation and conservative management of the same was carried out at his native place. Clinical examination revealed a distended abdomen with absence of bowel sounds. An X-ray of the abdomen (erect position) revealed prominent small and large bowel loops and multiple air–fluid levels. A CECT of the chest and abdomen did not show any mass or lesions in the abdomen. The patient was to be taken up for decompressive surgery. However, his clinical condition deteriorated rapidly with fever, hypovolaemic shock and multiorgan failure. He succumbed to the complications of intestinal obstruction at his

Table 1 Target volume and organs at risk prescription and the doses achieved with the IMRT plan

Parameters	Prescription	Dose achieved
Abdominal PTV		
D95%	30.60 Gy/17#	28.59
V95% (figure 2)		94 %
Homogeneity Index	0	0.42
Conformity Index	1	1.13
Organs at risk		
Single kidney*	Dmean < 12 Gy	18.51 Gy
	D15% < 18 Gy	29.94 Gy
Liver*	Dmean < 30 Gy	32.20 Gy
Urinary bladder*	Dmax < 65 Gy	32.19 Gy
Rectum*	Dmean < 40 Gy	12.0 Gy
Spinal cord*	Dmax < 45 Gy	24.65 Gy
Bowel*	Dmax < 54 Gy	37.96 Gy
	D15% < 45 Gy	33.45 Gy

Giving cognisance to the fact that adult radiation dose constraints cannot be applied as such to the younger population due to differential tissue development at different rates, the PENTEC (Paediatric Normal Tissue Effects in the Clinic) consortium is aiming to critically analyse radiation dose–volume effects on normal tissue tolerances and second cancer risk as a function of age/development in paediatric patients with cancer. At our institute, we have been using QUANTEC guidelines (pending the publication of PENTEC).

*Dose constraints adopted from QUANTEC.

#: fraction; Dmax, maximum dose to organ at risk; Dmean, mean dose to organ at risk.; Dx%, dose to x% of PTV/organ at risk; Gy, gray; IMRT, intensity-modulated radiotherapy; PENTEC, Pediatric Normal Tissue Effects in the Clinic; PTV, planning target volume; QUANTEC, Quantitative Analysis of Normal Tissue Effects in Clinic; Vx%, percentage volume of PTV/organ at risk receiving x%/x Gy dose.

native place 22 months after the initial diagnosis of his malignancy, but remained disease free.

DISCUSSION

Initially reported by Gerald and Rosai in 1989,² a reasonable number of cases of DSRCT have been reported until now, universally reporting an overall survival of 30%–55%³ with a median survival in the range of 17–25 months.⁴

Affecting an age range of 14–39 years and with a male predilection,⁵ it tends to be asymptomatic in early stages or may cause non-specific symptoms such as abdominal discomfort, pain or distension, nausea, vomiting, change in bowel habits, with a significant number of cases presenting with widespread dissemination to peritoneal surfaces of lungs, liver and lymph nodes.

CECT of the thorax and abdomen is the most widely used diagnostic modality characterised by multiple, bulky, nodular soft-tissue masses of variable sizes involving omental and serosal surfaces, without a distinct organ of origin.^{5,6} Pathology is characterised by expression of epithelial, neural, myogenic and mesenchymal markers.⁷

Our patient had this typical clinical and pathological presentation with IHC-confirmed diagnosis of metastatic DSRCT.

Surgical resection especially total radical resection or even debulking (removal of at least 90% of the tumour burden) has shown significant improvement in overall survival of advanced DSRCT.⁵ Two retrospective studies performed at the Memorial Sloan-Kettering Cancer Center have both found that aggressive surgical debulking of DSRCT is of prognostic significance.^{3,8}

However, majority of the cases are inoperable upfront and require induction chemotherapy. Systemic chemotherapy using the P6 protocol has an established role in inducing

Figure 2 Dose colour wash of intensity-modulated radiotherapy plan showing the 95% colour wash covering 94% of the planning target volume.

reasonable reduction of the tumour burden and facilitating surgical resection.¹

WAP-RT, after maximum surgical debulking was introduced at the Memorial Sloan-Kettering Cancer Center in an attempt to improve local control.¹ Conventional anteroposterior parallel opposed beams with kidney and liver blocks were used to deliver a total dose of 30 Gy with simultaneous boost to sites of gross residual disease. Apart from acute gastrointestinal and haematological toxicities, 33% of patients experienced long-term toxicity with bowel obstruction after surgical debulking and WAP-RT.⁹

In spite of the reported toxicities, in one of the largest series reporting 41 cases, a significant difference in median survival was noted (47 vs 14 months, respectively; $p=0.0147$) between patients who received WAP-RT and those who did not.¹⁰

Pinnix *et al* compared conventional three-dimensional plans with IMRT plans dosimetrically for organs at risk especially pertaining to bone marrow in eight patients. The mean bone doses were roughly 25% lower with the IMRT plan resulting in minimal haematological morbidity in contrast to the haematological toxicity documented in other series using two-dimensional/three-dimensional technique.¹¹

Desai *et al* compared the WAP-RT outcomes of nine patients treated with IMRT and a 22-patient two-dimensional RT cohort

reported small bowel obstruction in 11% for IMRT vs 27% for two-dimensional RT.¹²

IMRT allows conformal dose distribution to peritoneal surfaces in the abdomen and pelvis with the potential sparing of the organs at risk within their respective radiation tolerance. Further, simultaneous dose escalation to focal areas of gross residual disease may be attempted without increasing the overall treatment time.

The study by Desai *et al* remains the most important series evaluating radiotherapy for the treatment of DSRCT. A comparison cohort, however, was not available to quantify the improvement in survival after surgery.

Atallah *et al* performed a multicentric retrospective study to identify the prognostic impact of adjuvant abdominal radiotherapy. Overall survival and peritoneal progression-free survival (PPFS) were higher in the group receiving radiotherapy after any form of cytoreductive surgery compared with the group not receiving radiotherapy ($p=0.045$ and $p=0.006$, respectively). After complete cytoreductive surgery, radiotherapy improved PPFS ($p=0.024$) but differences in OS and Progression free survival (PFS) were not significant.¹³

Treatment with chemotherapy, surgery and radiotherapy confers a 3-year survival of 55% compared with 27% for those who do not receive all three modalities.³

In an effort to improve the dismal survival rates and reduce treatment-related morbidities, alternative treatment options which have shown promising results in other peritoneal malignancies have been investigated in DSRCT. Hyperthermic intraperitoneal perfusion with chemotherapy has been shown to improve survival in select group of patients.¹⁴

Thirty-two patients with intra-abdominopelvic DSRCT treated with sequential neoadjuvant chemotherapy, cytoreductive surgery, hyperthermic intraperitoneal perfusion with chemotherapy (HIPEC) and Whole abdominal radiotherapy (WART) were analysed. Remarkably improved median overall survival of 60 months was reported with a 3-year overall survival of 64%. However, this aggressive approach was associated with grade 3 or higher toxicities in 84% of patients. Severe late gastrointestinal toxicities (grade 4 or higher) occurred in two patients including a case of small bowel obstruction.¹⁵

Investigators have tried to identify targets for immunotherapy in DSRCT such as anti-IGF-1R antibody ganitumab, tumour-specific antigens including the disialoganglioside GD2 and the antigen recognised by the antibody 8H9 and lysine-specific demethylase. Early-phase trials with these are under way in an attempt to improve survival with reduced morbidity.^{16–18}

Though our patient could complete all the phases of treatment and remained disease free, resulting in a disease-free duration of 14 months after completion of radiotherapy, treatment-induced morbidity in the form of recurrent intestinal obstruction led to frequent visits to the hospital, additional investigations, a resurgery for adhesiolysis and finally resulting in mortality due to recurring morbidity.

The upper and lower gastrointestinal tracts are contained within the peritoneal cavity and are targets for radiotherapy regardless of the radiation therapy delivery technique.

More than 90% surgical debulking either before or after chemotherapy, complete or very good partial response to multimodality treatment, use of the P6 protocol, radiotherapy, intraperitoneal chemotherapy, age <30 years and patients treated after 2003 are the factors associated with improved survival in DSRCT.⁸ However, the probability of severe morbidity resulting from an aggressive multimodal approach

in paediatric population needs to be balanced against the zeal to achieve locoregional control and a long survival.

Learning points

- ▶ Desmoplastic small round cell tumour (DSRCT) is a rare and aggressive tumour with low overall survival rates.
- ▶ Whole abdominopelvic radiotherapy– intensity-modulated radiotherapy is an integral part of management of disseminated abdominal DSRCT.
- ▶ The small bowel radiation dose constraints need to be optimised further with avoidance of any hot spots on the bowel especially when dealing with a surgically handled bowel with multiple, confluent peritoneal and omental deposits.
- ▶ After an aggressive multimodal approach, long-term quality-of-life issues become pertinent requiring a close follow-up, documentation and reporting.

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