The UK Experience of a Treatment Strategy for Pediatric Metastatic Medulloblastoma Comprising Intensive Induction Chemotherapy, Hyperfractionated Accelerated Radiotherapy and Response Directed High Dose Myeloablative Chemotherapy or Maintenance Chemotherapy (Milan Strategy)

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INTRODUCTION

Medulloblastoma (MB) is a highly aggressive malignant posterior fossa brain tumor with a marked propensity to seed within the cerebrospinal fluid (CSF) pathways. Metastatic spread occurs in up to 35% of cases at diagnosis and these patients historically had a poor prognosis.[1,2] Despite the addition of chemotherapy to craniospinal radiotherapy (CSI) in the 1980s, large multicenter studies have reported 5-year progression-free survival (PFS) figures of between 30 and 40% and the optimal strategy remains controversial.[3–7] Recent studies are summarized in Table I and the best published results were in 2009 by Gandola et al.

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**Background.** Historically, the 5-year overall survival (OS) for metastatic medulloblastoma (MMB) was less than 40%. The strategy of post-operative induction chemotherapy (IC) followed by hyperfractionated accelerated radiotherapy (HART) and response directed high dose chemotherapy (HDC) was reported in a single center study to improve 5-year OS to 73%. We report outcomes of this strategy in UK. **Methods.** Questionnaires were sent to all 20 UK pediatric oncology primary treatment centers to collect retrospective data on delivered treatment, toxicity and survival with this strategy in children aged 3–19 years with MMB. **Results.** Between February 2009 and October 2011, 34 patients fulfilled the entry criteria of the original study. The median age was 7 years (range 3–15). Median interval from surgery to HART was 109 versus 85 days in the original series. The incidence of grade 3 or 4 hematological toxicities with IC and HDC was 83–100%. All 16 patients who achieved complete response by the end of the regimen remain in remission but only three of 18 patients with lesser responses are still alive (P < 0.0001). With a median follow-up of 45 months for survivors, the estimated 3-year OS is 56% (95% CI 38, 71). This result is outside the 95% CI of the original study results and encompasses the historical survival result of 40%. **Conclusion.** Within the limits of statistical significance, we did not replicate the improved survival results reported in the original series. The reasons include differences in patient sub-groups and protocol administration. International randomized phase III studies are needed. Pediatr Blood Cancer 2015;62:2132–2139.

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Abbreviations: CCLG, children’s cancer and leukemia group; CI, confidence interval; CR, complete response; CSA, craniospinal axis; CSF, craniospinal fluid; CSI, craniospinal irradiation; CTC, common toxicity criteria; HART, hyperfractionated accelerated radiotherapy; HDC, high dose chemotherapy; IC, induction chemotherapy; MB, medulloblastoma; MMB, metastatic medulloblastoma; MRI, magnetic resonance imaging; OS, overall survival; PD, progressive disease; PFS, progression free survival; PR, partial response; SD, stable disease; SE, standard error; TPN, total parenteral nutrition; UK, United Kingdom; VGPR, very good partial response

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<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Enrolment time (range)</th>
<th>Median age (range)</th>
<th>Regimen</th>
<th>Stage</th>
<th>Staging method</th>
<th>Complete response (CR) rate</th>
<th>Median follow-up (yrs)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bailey et al.[1]</td>
<td>29</td>
<td>1984–1989</td>
<td>6.6 (0–15)</td>
<td>IC (Procarb, Vinc, MTX) then RT then MC (Vinc, CCNU)</td>
<td>M1-8; M2-13; M3-8</td>
<td>Pre-op CT or myelogram; CSF cytology not taken into account; post-op myelography strongly recommended not mandatory; attempts to centrally review pathology and radiodiagnostic material</td>
<td>No info</td>
<td>6.3</td>
<td>3-yr EFS 43%</td>
</tr>
<tr>
<td>Zeltzer et al., Yao et al.[3,14]</td>
<td>90</td>
<td>1986–1992</td>
<td>6.9 (1.6–21.7)</td>
<td>Concomitant CRT (Vinc) then MC (Vinc, CCNU, Pred)</td>
<td>M1-32; M2-13; M3-43; M4-2</td>
<td>Pre-op CT, post op myelography, CSF cytology, bone marrow aspirate and biopsy ± MR brain and spine; central pathology review</td>
<td>No info</td>
<td>7</td>
<td>5-yr PFS -57% (M1) -40% (M2)</td>
</tr>
<tr>
<td>Kortmann et al.[15]</td>
<td>47</td>
<td>1991–1997</td>
<td>7.4 (3–17.8)</td>
<td>Arm 1 = 1 cycle of IC (Ifos, Etop, MTX, Cis, Cyta) then RT then MC Arm 1 = 1 cycle of IC (Ifos, Etop, MTX, Cis, Cyta) then RT then MC</td>
<td>M1-21; M2/3-26</td>
<td>Pre-op MRI used mostly, CT in early patients, post op CSF cytology, post op MRI or CT, central pathology review</td>
<td>Arm 1–41.6% CR in M2/3 Arm 2–85.7% CR in M2/3</td>
<td>2.5</td>
<td>3-yr RFS -65% (M1) -30% (M2/3) poor survival in both arms</td>
</tr>
<tr>
<td>Taylor et al.[2]</td>
<td>68</td>
<td>1992–2000</td>
<td>7.8 (2.8–16.4)</td>
<td>IC (Vinc, Etop, Carbo, Cyclo) then RT</td>
<td>M2-13; M3-55</td>
<td>Spinal MR or myelogram prior to and within 2 weeks of surgery, CT or MR brain within 48-72hr of surgery, scans not centrally reviewed, CSF sampling recommended not mandatory (12 patients)</td>
<td>39% CR</td>
<td>7.2</td>
<td>5-yr EFS 35% 5yr OS 44%</td>
</tr>
<tr>
<td>Gajjar et al.[16]</td>
<td>42</td>
<td>1996–2003</td>
<td>6.6 (3.1–17)</td>
<td>RT then dose-intensive chemo (Cis, Vinc, Cyclo)</td>
<td>M1-9; M2-6; M3-27</td>
<td>MRI brain and spine, and CSF assessed at least 10 days after resection, post op MRI brain within 48 hr of surgery, central pathology review</td>
<td>57% CR</td>
<td>5</td>
<td>5-yr PFS 66%</td>
</tr>
<tr>
<td>Gandola et al.[8]</td>
<td>33</td>
<td>1998–2007</td>
<td>10 (3.2–34)</td>
<td>IC (MTX, Vinc, Carbo, Cyclo, Etop) then HART then MC (Vinc, CCNU) or HDC (Thiotepa)</td>
<td>M1-9; M2-6; M3-17; M4-1</td>
<td>Brain and Spine MRI pre and post op, CSF cytology weeks after surgery at the earliest, central pathology review</td>
<td>91% CR</td>
<td>6.8</td>
<td>5-yr OS 73% 5-yr PFS 72% 3-yr OS 77%</td>
</tr>
<tr>
<td>Allen et al.[17]</td>
<td>69</td>
<td>1996–2003</td>
<td>7.8 (3–20)</td>
<td>IC (1st, 3rd and 5th cycles - Cis, Etop, Cycs, Vinc; 2nd and 4th cycles - Carbo, Etop) then HART</td>
<td>M1-3-69</td>
<td>Brain and spine MRI, preferably within 72 hr after surgery, and CSF cytology within 2–3 weeks after surgery. Bone marrow aspirate and bone scan optional. Central review of pathology</td>
<td>66% CR or PR or SD after chemo</td>
<td>7.9</td>
<td>5-yr PFS 36% 5-yr OS 49%</td>
</tr>
<tr>
<td>Study</td>
<td>Number of patients</td>
<td>Enrolment time (range)</td>
<td>Median age (range)</td>
<td>Regimen</td>
<td>Stage</td>
<td>Staging method</td>
<td>Complete response (CR) rate</td>
<td>Median follow-up (yrs)</td>
<td>Outcome</td>
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<tr>
<td>Jakacki et al.[13]</td>
<td>77</td>
<td>1998–2004</td>
<td>8.7 (3.1–21.6)</td>
<td>Concomitant (Vinc, Carbo) CRT then MC - Regimen A MC - 6 months of Cyclo Vinc Regimen B MC - Cis added to Regimen A</td>
<td>M1-18; M2-10; M3-49</td>
<td>Pre and post op MR brain and spine, CSF cytology, central review of pathology</td>
<td>No info</td>
<td>8.5</td>
<td>5-yr PFS 71%</td>
</tr>
<tr>
<td>Taylor et al.[18]</td>
<td>34</td>
<td>2002–2008</td>
<td>7.7 (0.4–15)</td>
<td>HART with concurrent chemo (Vinc) then MC (Vinc, CCNU, Cis)</td>
<td>M1-9; M2-3; M3-22</td>
<td>Pre op MR or CT brain, spinal MRI, post op imaging within 3 days of surgery, CSF cytology within 15–21 days of surgery, central review of pathology and scans</td>
<td>No info</td>
<td>4.5</td>
<td>3-yr EFS 59%</td>
</tr>
<tr>
<td>Tarbell et al.[19]</td>
<td>108</td>
<td>1990–1996</td>
<td>7.8 (3–21.4)</td>
<td>Arm 1 – RT then chemo (Cis, Etop) then MC (Vinc, Cyclo) OR Arm 2 - IC (Cis, Etop) followed by RT then MC (Vinc, Cyclo)</td>
<td>M1-29; M2-36; M3-34; M4-9</td>
<td>CT or MRI within 72 hr of surgery or between 10 and 21 days after surgery, CSF cytology, central review of pathology</td>
<td>Arm 1–22% CR Arm 2–17% CR</td>
<td>6.4</td>
<td>3-yr OS 71% 5-yr EFS Arm 1–64% Arm 2–51%</td>
</tr>
<tr>
<td>UK experience of Gandola et al. regimen</td>
<td>34</td>
<td>2009–2011</td>
<td>7 (3–19)</td>
<td>IC (MTX, Vinc, Carbo, Cyclo, Etop) then HART then MC (Vinc, CCNU) or HDC (Thiotepa)</td>
<td>M1-6; M2-12; M3-16; M4-0</td>
<td>MRI brain and spine pre and post op; CSF cytology</td>
<td>47% CR</td>
<td>3.8</td>
<td>3-yr OS 56%</td>
</tr>
</tbody>
</table>

Carbo, carboplatin; CCNU, lomustine; chemo, chemotherapy; Cis, cisplatin; CR, complete response; CRT, chemoradiotherapy; CSF, cerebrospinal fluid; Cyclo, cyclophosphamide; Cytar, Cytarabine; EFS, event free survival; Etop, Etoposide; HART, hyperfractionated accelerated radiotherapy; HDC, high dose chemotherapy; hydroxy, hydroxyurea; IC, induction chemotherapy; Ifos, ifosfamide; info, information; MC, maintenance chemotherapy; Methypred, methylprednisolone; MTX, methotrexate; OS, overall survival; PD, progressive disease; PFS, progression free survival; post op, post-operative; pre op, pre-operative; PR, partial response, Procarb, procarbazine; RT, radiotherapy; SD, stable disease; Vinc, vincristine; yrs, years.
who reported a 5-year PFS and overall survival (OS) of 72 and 73% respectively in 33 patients using the so-called “Milan strategy.”[8]

Based on the results of this single center study the Children’s Cancer and Leukemia Group (CCLG) published treatment guidelines for children over 3 years of age with metastatic MB (MMB). We have conducted a retrospective multicenter study to compare the survival and toxicity results of the UK patients having been treated de novo for MMB according to these guidelines since 2009 with those published by the Milan group.[8]

**METHODOLOGY**

**Eligibility**

We collected survival and toxicity data for all newly diagnosed patients older than 3 years at the time of surgery with histologically proven MMB who fulfilled the eligibility criteria for the original series by the Milan group.[8]

**Treatment Delivered**

The planned regimen was as described by Gandola et al. and involved post-operative induction chemotherapy (IC) within 3 weeks of surgery.[8] IC also facilitated stem cell harvest for two sequential autologous transplants. Craniospinal axis (CSA) hyperfractionated accelerated radiotherapy (HART) was commenced 3–4 weeks after IC and involved twice daily irradiation to CSA followed by a boost to the primary site and sites of all macroscopic residual disease with a minimum time interval between all fractions of 6 hr. The standard CSA HART dose was 39 Gy in 30 fractions with a boost to the posterior fossa of 21 Gy in 14 fractions. Macroscopic residual lesions received an additional 9 Gy in six fractions. Patients under 10 who achieved complete response (CR) prior to HART received a lower CSA dose of 31.2 Gy in 24 fractions with a boost dose of 28.5 Gy in 19 fractions. Those who achieved CR or very good partial response (VGPR) with no residual tumor cells in the CSF and only a single residual metastatic lesion on MRI received maintenance chemotherapy (MC) 4 weeks later. Patients who did not achieve CR or VGPR after IC commenced high dose consolidation chemotherapy (HDC) 4 weeks after completion of HART. Two cycles of Thiotepa were planned with autologous stem cell reinfusion carried out at day 5 of each Thiotepa cycle.

**Registration Questionnaire**

We issued a registration questionnaire to Radiation Oncologists at all 20 CCLG centers with centralized specialist care for children with cancer to identify patients treated with the above strategy in the UK between February 2009 and 31st October 2011. Unique study numbers were created for each patient to anonymize the data. As the study was a service evaluation, formal ethics approval was not required.

**Detailed Questionnaire for Deliverability and Toxicity Data**

A follow-up questionnaire requested data on patient demographics, disease status at diagnosis (Chang’s staging system), treatment administered, acute toxicity of therapy and delays in treatment.[9] Data were collected on the response of the tumor at each step of the treatment regimen, event free and overall survival, and late neurotoxicity. Due to the difficulty in collecting retrospective toxicity data, the focus was on collecting data regarding febrile neutropenia, platelet and red cell transfusion, and total parenteral nutrition (TPN) rates as these are objective events recorded in the hospital record. Other common toxicity criteria (CTC) 4.0 grade 3 or 4 toxicities were also recorded.[10] Response at the end of each stage of treatment was classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD).[11] Anonymized scan and CSF results were returned with the questionnaire.

**Data Analysis and Statistics**

The data were analyzed using SPSS software. PFS and OS were calculated using the Kaplan–Meier method, from the start of IC (similar to Gandola et al.) censoring data for progression and survival at the latest follow-up.[8,12] The log rank test was used to test significance of differences in survival between groups of patients.

**RESULTS**

**Patient Characteristics**

Thirty-four patients were identified who fulfilled the entry criteria of the original publication,[8] having been treated de novo for MMB, in 14 of 20 UK pediatric oncology centers; the other six centers had chosen not to use the regimen or did not treat any patients who fulfilled the entry criteria of the original publication during this period. Survival data were updated till 14th September 2014. Median and mean follow-up of survivors was 45 months and 47 months, respectively (range 35–63 months). The patient characteristics of the UK cohort are shown in Table II.

**Protocol Delivery Compliance**

**Induction chemotherapy (IC).** Data were available for 32 patients regarding deliverability of IC. IC was to be delivered within 21 days of surgery but there was an extra delay of more than a week in 38% of patients (Table III). The median delivery time was 51 days which is slightly longer than the recommended 49 days. Eighty-seven percent completed IC within 1 week of target. Ninety-one percent of patients received all planned IC drugs; however only 79% completed IC without any dose reductions, and only 30% completed IC without any dose reductions or delays. Week 2

**TABLE II. Characteristics of Patients in the UK and Milan Groups**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>UK</th>
<th>Gandola et al.[8]</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>34</td>
<td>33</td>
</tr>
<tr>
<td>Median age</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Age range</td>
<td>3–19</td>
<td>3.2–34</td>
</tr>
<tr>
<td>Female: Male</td>
<td>10: 24</td>
<td>7: 26</td>
</tr>
<tr>
<td>M1</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>M2</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>M3</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td>M4</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Anaplastic/Large cell</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

*Pediatr Blood Cancer DOI 10.1002/pbc*
TABLE III. Planned and Actual Delivery Times and Time Intervals Between Each Stage of Treatment

<table>
<thead>
<tr>
<th></th>
<th>Ideal timing according to protocol</th>
<th>Actual time (range)</th>
<th>Delivered according to plan</th>
<th>Delayed by more than 1 week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery to start of induction chemo</td>
<td>Within 21 days</td>
<td>24 (12–64) days</td>
<td>41%</td>
<td>38%</td>
</tr>
<tr>
<td>Induction chemo delivery time</td>
<td>49 days</td>
<td>51 (45–64) days</td>
<td>30%</td>
<td>13%</td>
</tr>
<tr>
<td>End of induction chemo to start of HART</td>
<td>21–28 days</td>
<td>29 (14–51) days</td>
<td>Within 28 days = 47%</td>
<td>&gt;35 days = 20%</td>
</tr>
<tr>
<td>HART delivery time</td>
<td>Range 30–32 days</td>
<td>29 (25–35) days</td>
<td>97%</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Etoposide was delayed in six patients, Week 5 chemotherapy was delayed in six patients, and Week 8 chemotherapy was delayed in two patients due to toxicity. There were no dose reductions up to week 5. Ten patients had significant dose reductions of 50% or more at some stage during IC.

HART. One patient died of progressive disease prior to HART, so 33 of 34 patients received HART. Another patient died after completion of HART due to PD prior to starting chemotherapy. The recommended interval from surgery to start of HART is within 91–98 days but our median interval was 109 days (range 77–160 days). Only 10 patients (30%) started HART within the recommended 98 days from surgery. The ideal HART delivery time is 30–32 days and our median HART delivery time was 29 days (range 25–35 days). Only 25 of 33 patients (76%) completed HART as planned (i.e., without dose changes or significant delays). One patient was delayed by 5 days, one patient by 2 days, and seven patients by 1 day. All 33 patients received the recommended CSI dose, but the posterior fossa and metastases boost doses were lower for seven patients (21%): two patients had 51 Gy to posterior fossa, one patient had 54 Gy to posterior fossa and 5.2 Gy boost to metastases, one patient had 48 Gy to posterior fossa and 12 Gy boost to metastases, two patients had 4.5 Gy boost to metastases, and one patient had 9.1 Gy boost to metastases. The reason for this is unclear.

High dose chemotherapy (HDC). Thirteen of 34 patients who failed to achieve CR or VGPR after IC went on to HDC after HART.

Of these 13 patients, seven patients received two cycles of HDC. Thiotepa, four patients received a single cycle of Thiotepa, and two patients received alternate agents due to lack of availability of Thiotepa in the UK (one patient had one cycle of Carboplatin, and Etoposide, and one patient had Carboplatin alone). Three patients who fit the criteria for HDC did not receive it: one patient died shortly after completion of HART; however the reasons are unclear regarding the other two patients.

Maintenance Chemotherapy (MC). Nineteen of 34 patients had MC, although the details were difficult to gather as this was mostly delivered in local hospitals. One patient had both HDC and MC.

Toxicity

There were no reported toxic deaths.

IC. The febrile neutropenia rate and red cell transfusion rates were 90%, platelet transfusion rate was 83%, and the TPN usage rate was 30%. The other grade 3 toxicities included two cases of vomiting and diarrhea, one case of mucositis, reaction, and nausea. There was one case of grade 4 hypokalemia.

HART. Acute grade 3 or 4 toxicity data were available on 30 patients. The febrile neutropenia rate was 9%, red cell transfusion rate was 63%, platelet transfusion rate was 28%, and TPN usage rate was 19%. Other grade 3 toxicities included one case each of esophagitis, mucositis, vomiting, diarrhea, and skin toxicity.

HDC. Toxicity data were available for ten of the 13 patients treated with HDC. The febrile neutropenia rate was 100%, red cell and platelet transfusion and TPN infusion rates were 90%, and fungal infection rate was 50%. Other grade 3 toxicities included four cases of mucositis, one case of diarrhea, and one case of allergic reaction.

MC. Data were available on nine of 19 patients who received MC. It was well tolerated with minimal acute toxicity. Febrile neutropenia rate was 22%, red cell transfusion rate was 44%, platelet transfusion rate was 11%, and no patients needed TPN.

Neurotoxicity. Late neurotoxicity data were available in 17 of 19 survivors. Eight patients have ataxia, two patients have hemiparesis, two patients have nystagmus, two patients have cranial nerve palsy, and one patient has dysconjugate eye movement. Eight patients have no reported neurotoxicity. Only three of the nine patients with neurotoxicity have had HDC: one patient had one cycle of Carboplatin, and two patients had two cycles of Thiotepa. We were unable to differentiate between neurological deficits due to the tumor effect at presentation, postoperative deficits, and chemotherapy- and radiotherapy-related neurotoxicity.

Response to Therapy (Fig. 1)

Response to IC. Ten of the 34 patients achieved CR post IC. One patient progressed and died during IC.

Response to HART. Post HART, one of the ten patients who achieved CR post IC progressed. HART induced further four CRs.

Response to HDC. There were four patients in SD and four patients in PD after IC. Of these eight patients with a clear indication for HDC, only five received HDC after HART. Of the four patients with SD, three had HDC and one had maintenance chemotherapy (and is still alive). Of the four patients with PD, two had HDC, one had maintenance chemotherapy after achieving a PR after HART but died at 22 months, and one died of PD one month after HART. Three of 13 patients who failed to achieve CR after HART achieved CR after HDC; of those who developed CR, two patients had two cycles and one patient had one cycle of HDC.

Overall Response and Survival

Figure 1 shows progress through therapy and response status. All 16 patients who achieved CR at the end of the regimen remain alive and in remission but only three patients with lesser responses (two patients with PR, one patient with SD) are still alive (P < 0.0001). The PFS and OS was 56% (95% CI 38–71%) at 3 years (Fig. 2). The median time from start of IC to disease progression was 11 months (range 2–14). After progression, the
Fig. 1. Response to different stages of the Regimen in UK and Milan. CR, complete response; PR, partial response; SD, stable disease; PD, progression of disease; ?, unknown response to the stage of treatment.

Fig. 2. Kaplan–Meier curves demonstrating progression free survival (PFS) and the overall survival (OS) for UK group treated with Milan Strategy (M. Medulloblastoma = Metastatic Medulloblastoma).

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median survival was 2 months (range 1–6). The differences in survival between the M-stages were not statistically significant.

**Effect of CR Rates on Survival**

OS was significantly better for patients who achieved CR at the end of treatment than those who did not (PR, SD, PD) (log-rank test P-value 0.0108). OS was also significantly better for patients who are responders (CR or PR) than non responders (SD or PD) at the end of treatment (log-rank test P-value 0.0255). There was a suggestion that CR rates are affected more by delays from IC to start of HART than surgery to start of IC, but the numbers are too small to draw firm conclusions.

**DISCUSSION**

Table I demonstrates staging methods, stages, response rates, and survival outcomes of recent studies using alternate regimens in comparison with the UK experience of Milan Strategy described by Gandola et al.[8] These studies range in size from 29 to 108 patients with 5-year results ranging from 35% EFS to 71% PFS with wide 95% confidence intervals (CI). The improved results in recent series may reflect the more rigorous application of staging with craniospinal MRI and craniospinal fluid cytology as shown in Table I. This can result in stage migration with an apparent improvement in outcome.[20]

With median follow-up of survivors of 45 months (range 35–63 months), we estimate 3-year OS of 56% (95%CI 38%, 71%). Gandola et al. reported estimated 3-year OS of 77% (95%CI 61, 93). [8] Therefore, the results reported by Gandola et al. were not reproducible in the UK multicenter setting, as our experience is outside the 95%CI of Gandola et al. and our 95%CI encompasses the historical result of 40% (Fig. 2).[8] The reason we could not replicate the results published by Gandola et al. may be due to chance (expressed as the wide 95%CI for both series), or due to multiple factors such as differences in patient characteristics, case selection, treatment delivery, and the nation-wide implementation of a regimen previously tested in a single center.[8]

The UK cohort of 34 patients was accrued in two and a half years at 14 hospitals treating according to a common nationally recommended protocol based on the regimen used by Gandola et al.[8] Gandola et al. cohort of 33 patients were recruited in 9 years. The UK accrual time is shorter reflecting the regimen being more readily accessible to patients in multiple centers across UK. This may have led to less selection bias in the UK series compared to the original series[8] where patients were treated from across the country at a single center, possibly resulting in less fit patients being selected out due to longer travel requirements than in UK.

We found a number of differences in the way that the treatment was delivered in the UK group compared to the prescribed protocol. Some elements of treatment were delayed and there was some non-compliance with doses. There were unexplained deviations that were non-compliant with the principles of the protocol such as not all poor responder receiving HDC (three patients) in the UK. However, the protocol was only amended to include HDC after the first nine patients had been treated and two early relapses observed in the original series. Only 76% of the UK patients completed HART as planned (i.e., without dose changes or significant delays) compared to 97% in the original series reported to have complete HART as planned, though the definition of this is unclear.[8]

The median interval between surgery and start of IC was longer in the UK cohort (Table III) (109 days (range 77–160 days) than the original series (85 days)).[8] This delay may reflect the longer post-operative recovery period required for the higher proportion of younger patients in the UK group than in the original series.[8] Previous studies have suggested that the outcome for medulloblastoma is worse in younger patients.[6,15,21] Additionally studies have suggested that more aggressive surgery could lead to more complications and that a delay from surgery to start of radiotherapy can affect survival.[15,22,23] More patients under the age of 10 in the UK cohort had complete resections than older patients. The mean interval between surgery and induction chemotherapy was 29 days (range 13–64 days), and 28 days (range 15–35 days) in patients under 10 who had complete resections and subtotal resections, respectively. This slightly longer recovery periods may contribute toward the lower CR rates seen in this age group. This raises the issue whether younger patients would benefit from less aggressive surgery as achieving surgical complete resections of the primary site may not be as important a predictive factor for survival as others in patients with metastatic disease.[2,13]

Our results suggest that delays from IC to start of HART may have a greater impact on CR rates than other delays but our numbers are too small to draw firm conclusions. It has been argued that an IC approach may have the advantage of allowing clinicians to start adjuvant therapy earlier and to reduce the burden of disease at the time of radiotherapy. However, intensive IC results in RT delays and poorer results as noted in some studies.[6,14,15] This remains an important unanswered question.

There were no treatment-related deaths in our cohort, whereas there was one reported toxic death in the original series.[8] We found the IC and HDC stages more toxic than reported in the original series.[8] The HART and maintenance chemotherapy toxicities cannot be compared to the original series as toxicity was not clearly described in the original publication.[8] The median time from start of IC to disease progression was similar in both the UK and the original series (11 months [range 2–14] and 12 months [range 5–48], respectively). [8] After progression, the median survival in our patients was 2 months (range 1–6) compared to 5 months (range 1–23) in the original series.[8] This poor outcome after relapse highlights the importance of selecting a first line regimen with the best survival outcomes and toxicity rates.

The CR rate after IC was 10/34 (29%) in our series and 12/33 (36%) in the original series.[8] HART induced further four CRs in our series and 14 CRs in the original series.[8] HDC induced an additional three CR in our series and four CR in the original series.[8] The CR rates at the end of treatment were lower in our series16/34 (47%) compared to 30/33 (91%) in the original series (Fig. 1).[8] In our series, PFS and OS were significantly higher in patients who achieved CR than no CR at the end of treatment, and the lower CR rates in our series will contribute toward the lower survival rates. Gandola et al. have also shown a similar association between better survival and higher CR rates.[8] In some studies, CR rates were neither reported nor its association with survival described (Table I). We assume that the differences in the way the treatment was delivered possibly due to high rates of toxicity in our series may be one of the reasons for the difference in CR rates and outcomes seen in the UK cohort. We could not determine in this retrospective study why these deviations occurred, as there was no compliance monitoring with the protocol until after these 34 patients were treated.
Our retrospective study results were fed back to the centers but it is unclear how this information was interpreted. Subsequently, another retrospective study by a different group exploring neurotoxicity associated with this regimen in a separate UK cohort of patients including supratentorial primitive neuroectodermal tumors has discovered cases of severe and disabling neurotoxicity (three cases of severe myelitis and seven cases of severe global neurotoxicity with one death) in children who received thiotepa following HART.[23] Such adverse outcomes are rare and were not observed in our series of metastatic medulloblastoma patients treated with the same regimen nor in the original series.[8] This protocol was discontinued (since July 2014) in the UK due to lower than expected survival outcomes and concerns regarding neurotoxicity found in the second UK cohort.[24]

CONCLUSION

Our retrospective study could not replicate the results obtained at a single center when delivered at a national level. This study highlights the importance of careful guideline development and the need for higher standards of compliance and toxicity monitoring prospectively when implementing a regimen from a single center study across multiple centers at a national level. The future priority should be to strengthen international collaboration to develop phase 3 studies to compare the different chemo-radiation regimens for this group of patients with poor prognosis.

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