A Phase 3 Trial of Biologically-Based Therapy Reduction for Intermediate Risk Neuroblastoma

Neuroblastomas account for 15% of cancer-related deaths occurring in childhood. The children's cancer group study (CCG) 3881 showed that the chances of overall survival (OS) were greater than 80% with aggressive chemotherapy and surgery. While these results are encouraging, the burden of treatment is quite severe in these young patients. The primary goal of this trial (COG 3961) was to achieve a 3-year OS >90% for intermediate risk (IR) neuroblastoma with reduced therapy, and hopefully toxicity, compared to historical controls.

Treatment was administered on an outpatient basis using the most active agents available for neuroblastoma. Standard therapies were modified, however, with the aim of reducing toxicity: cisplatin was replaced with carboplatin and the total dose of anthracyclines were limited to a cumulative dose of below 100mg/m^2. Patients were stratified according to favorable or unfavorable biology; treatment was administered over 64 days in the favorable group with 4 cycles, and over 168 days in the unfavorable group with 8 cycles.

Between March of 1997 and May of 2005, 463 eligible patients were enrolled in the study; roughly 70% had favorable biology and 30% had unfavorable biology. Fifty-six (56) percent of the patients had stage III disease (105 children and 156 infants), 37% were infants with stage IV disease and 7% were infants with stage IV-S disease. The study was designed such that patients with favorable biology were to receive 4 cycles of treatment, but if they did not achieve a response during this time, they were then eligible to receive all 8 cycles; 40% of patients in the favorable biology group did so.

Again, one of the goals of this study was to reduce overall toxicity. Reversible hematological toxicities were seen in 69% of the patients. Importantly, however, renal, cardiac and hearing toxicities were observed in less than 2% of the patients, if transient grade 3/4 toxicities in blood pressure were excluded. Non-hematological toxicities were significantly less in course two than in course one, which is almost certainly related to the release of disease burden by the end of course one. Finally, deaths due to infection were low at 0.8%.

Response rates (comprised of complete response, very good partial response, and partial response) were achieved in 85% of patients in the favorable biology group and 89% of the unfavorable biology group. In both groups, 3-year OS was achieved in over 90% of the patients (Figure 1).

Figure 1. 3-Year Event Free Survival and Overall Survival in the Favorable Biology Group, the Unfavorable Biology Group and in Both Groups Combined.

- CR/VGPR/PR achieved in 85% (favorable biology) and 89% unfavorable biology)
- 50 (11%) events including 15 deaths and 2 secondary AML

Cohort	n	3 Yr EFS	3 Yr OS
Overall	467	88 ± 2%	96 ± 1%
Favorable Biology	330	90 ± 2%	98 ± 1%
Unfavorable Biology	137	83 ± 3%	94 ± 2%

Highlights from the **American Society of Clinical Oncology Annual Meeting 2007**

The primary hypothesis of this study, therefore, was confirmed, with 3-year OS >90% for intermediate risk neuroblastoma. More importantly, compared with the historical control CCG 3881, this outcome has been achieved with a very significant reduction in therapy (Table 1). Future phase 3 trials will prescribe duration of therapy, at least in part, in accordance with the results of this trial.

Table 1. Overall Survival and Treatment Burden in CCG 3881 and COG A391.

Protocol	Length of Therapy (Days)	Reduction (%)	Treatment Days	Reduction (%)
3881	268		71	
3961				
Favorable	84	70%	10	85%
Unfavorable	168	40%	18	75%

Outcome of Children Less Than Three Years Old at Diagnosis with Non-Metastatic Medulloblastoma Treated with Chemotherapy on the "Head Start" I and II Protocols: Final Report

The majority of malignant brain tumors in children develop within the first 6 years of life. The most common type is medulloblastoma (MB), an aggressive tumor which grows rapidly, recurs often and is susceptible to metastasis. The standard of care for older children with medulloblastoma is radiation therapy, followed by chemotherapy. However, this treatment is often associated with several adverse effects, including learning and attention difficulties, short-term memory deficits, social adjustment problems, hearing, speech and language problems, and impaired physical growth. Therefore, a strategy to treat this type of disease without radiation is evident; the goals of Head Start I and II were to address this issue.

The treatment plan was the same in both protocols. After maximum surgical resection, patients underwent 5 cycles of induction chemotherapy, followed by an extensive disease evaluation. If the analysis showed residual tumor, the investigators encouraged a re-resection; if the patients progressed by this time, they were removed from the study. Patients who were either stable at the end of induction, or had responsive disease, underwent consolidation chemotherapy with autologous hematopoietic stem cell rescue. Finally, patients with no evidence of disease after these treatments (the majority of patients in this trial) did not receive radiation.

Twelve (12) patients were treated in Head Start I and 9 patients were treated in Head Start II. The male and female ratios were similar in both studies, though patients tended to be younger in Head Start I. Gross total resection was more successful in Head Start II. Three (3) patients in Head Start I and 6 patients in Head Start II were desmoplastic. Event-free survival (EFS) for all patients in the cohort was 52% at 5 years, while the overall survival (OS) was 70% at 5 years.

The investigators dissected the data according to the prognostic factors. The EFS when classified by extent of resection is shown in Figure 1 and desmoplastic vs classical MB is shown in Figure 2. Although these results were not statistically significant, a gross total resection and desmoplastic MB did trend toward improved EFS; OS did not show this same trend. The total radiotherapy-free survival among the surviving patients in this study was 73%.

Figure 1. EFS by Extent of Resection in Head Start I and II.

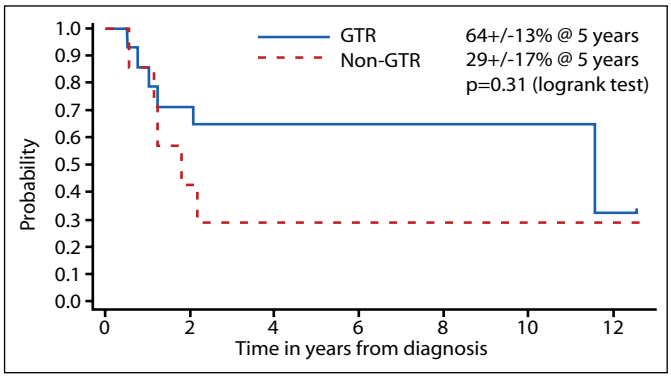
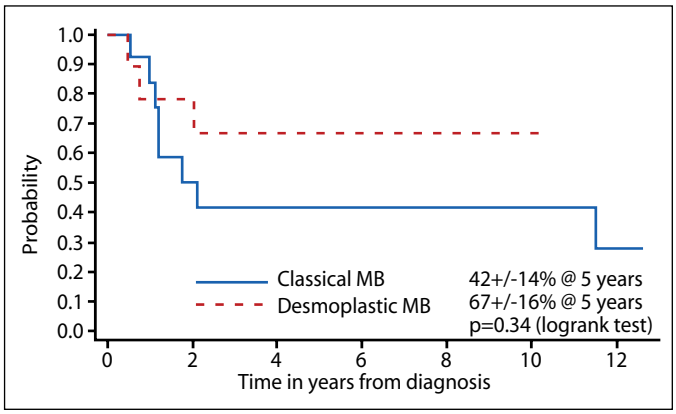


Figure 2. EFS Characterized by Desmoplastic or Classical MB in Head Start I and II.



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Despite the success of UCBT in children, this strategy does not work as well for adults due to low cell doses and mismatches. A new strategy of using a double UCB platform seems to markedly increase the eligibility of adults for UCBT and appears to positively impact survival. Additionally, nonmyeloablative therapy clearly extends the eligibility with a low incidence of transplant-related mortality. Finally, a new approach that is being developed is to reduce non specific SC losses and optimize homing by direct injection into the pelvis (the BM microenvironment).

In conclusion, allogenic SCT is a viable option for patients without an exact match. Alternatively, recent data has shown that unmatched CB has greater success than either BM or PBSCs that are unmatched. Furthermore, UCBT is the standard of care in children, but the double UCB platform and nonmyeloablative therapy has markedly extended the use of UCBs in adults. It seems that interest in UCB will not wane in the near future as more benefits and applications are being realized.

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only 54%, according to Dr. DeMatteo's earlier research (*Ann Surg* 2000). DeMatteo and colleagues hypothesized that adjuvant imatinib would prolong RFS following the complete resection of primary GIST.

The main entry criterion was primary GIST size of ≥3 cm. All patients had complete gross resection of KIT+ tumors and were randomized to a year of either placebo or of 400 mg daily of imatinib. The endpoints were recurrence-free survival (RFS, primary), overall survival (OS, secondary) and safety. Progressing patients were unblinded and switched from placebo to imatinib 400 mg or from 400 imatinib to 800 mg/day.

After the third scheduled 6-month analysis, with 644 of a planned 732 patients enrolled, the trial was stopped prematurely. Similar percentages of the prescribed dose were delivered to both groups (placebo 71%, imatinib 67%), with tumor recurrence (38% placebo, 1% imatinib) and toxicity (7% placebo, 50% imatinib) the main causes, respectively, of dose alterations. Grade 3-4 toxicities with imatinib were mainly neutropenia, liver function test elevations, skin rash and edema.

OS was similar in both groups, with a surprisingly small number of events (4 deaths placebo, 3 deaths imatinib, p=0.72), Dr. DeMatteo said. Six (6) were attributed to disease recurrence. For the primary PFS endpoint at 1-year, there were 62 events in the placebo arm and 21 in the imatinib arm (83% vs 97%, p=0.001). Dr. DeMatteo pointed out that at about 6 months after the completion of treatment the RFS slope began to turn downward.

Subgroup analysis showed stronger imatinib effects in patients with the largest tumors (≥10 cm), with RFS of 67% in the placebo arm and 96% in the imatinib arm (p=0.001), and a descending PFS slope at about a year and one-half.

Dr. DeMatteo concluded, "One-year of 400 mg/day imatinib mesylate is safe and well-tolerated after the complete resection of a primary gastrointestinal stromal tumor. Recurrence-free survival is increased. Overall survival has not been altered at this time with these preliminary data."

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There were 3 toxic deaths in Head Start I and 1 in Head Start II. Five (5) patients relapsed in Head Start I, whereas only 2 patients did so in Head Start II; all relapses developed within 25 months and the majority occurred locally. Overall quality of life (QoL) was within the average range at both times of assessment (70 months and 124 months); younger patients displayed fewer behavioral problems and higher adaptive function at both time points.

In conclusion, EFS in this study mirrors those reported in the German HIT study [Rutkowski et al. *New Eng J Med* 2005]. Incomplete resection and absence of desmoplasia trend toward inferior EFS, but not OS. These results show that, despite administering the myeloablative chemotherapy, these patients can be retrieved with either more chemotherapy or irradiation. Although the number of patients is limited in these studies, the QoL was within the normal range in the Head Start I study and it was improved in 3 out of 4 patients in the Head Start II study.

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