Disclosures

- Amy Newman and Shari Feinberg have no industry relationships relevant to this presentation
- Off label use will be discussed

COG Disclosure

The information in this presentation is intended for educational purposes only and is solely for the use of the individual nurse learner. This information is not intended as the sole source of guidance in providing Children’s Oncology Group (COG) protocol-directed nursing care, and current COG protocols should always be consulted prior to making patient care decisions for any patient enrolled on a COG protocol. Learners should also be aware that COG protocols are research plans designed to investigate particular study questions, that recommendations for treatment and dosing are made within the context of specific research aims, and that these recommendations are intended only for use within a structured research setting. Although every attempt has been made to assure that the informational content contained herein is as accurate and complete as possible as of the date of presentation, no warranty or representation, express or implied, is made as to the accuracy, reliability, completeness, relevance, or timeliness of this content. This information may not be copied or redistributed in any form, or used for any purpose other than nursing education.

Abbreviations

<table>
<thead>
<tr>
<th>Liver function tests</th>
<th>LFT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of heterozygosity</td>
<td>LOH</td>
</tr>
<tr>
<td>Lymph node</td>
<td>LN</td>
</tr>
<tr>
<td>Maximum tolerated dose</td>
<td>MTD</td>
</tr>
<tr>
<td>Memorial Sloan-Kettering Cancer Center</td>
<td>MSKCC</td>
</tr>
<tr>
<td>Peripheral intravenous line</td>
<td>PIV</td>
</tr>
<tr>
<td>Pneumocystis Carinii</td>
<td>PCP</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>RMS</td>
</tr>
<tr>
<td>Subsequent malignant neoplasm</td>
<td>SMN</td>
</tr>
<tr>
<td>Temozolomide</td>
<td>TMZ</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>TMP</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>UTI</td>
</tr>
<tr>
<td>Vincristine, dacarbazine, cyclophosphamide</td>
<td>VAC</td>
</tr>
<tr>
<td>Vincristine, dacarbazine, ifosfamide</td>
<td>VAI</td>
</tr>
<tr>
<td>Vincristine, doxorubicin, cyclophosphamide</td>
<td>VACOP</td>
</tr>
<tr>
<td>Vincristine, ifosfamide, etoposide</td>
<td>VIF</td>
</tr>
<tr>
<td>Vincristine, ifosfamide, temozolomide</td>
<td>VIT</td>
</tr>
</tbody>
</table>

Objectives

- At the end of this activity, the learner will be able to...
  - Identify the overall treatment strategy for patients with rhabdomyosarcoma (RMS)
  - Describe the basic outline of treatment according to the current High-Risk RMS protocol, ARST08P1, in lay language
  - Identify possible side effects of the anti-IGF-IR monoclonal antibody, IMC-A12, utilized in this protocol
  - List common acute and late effects associated with treatment for RMS
Epidemiology & Risk Stratification

Risk Group Stratification

- Schema attempting to match treatment intensity to prognosis
- Relies on tumor characteristics before therapy and results of surgical intervention
- Incorporates
  - Site
  - Staging
  - Histology
  - Clinical Group

Definitions

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
</table>
| Favorable  | • Orbit (non parameningeal head and neck)  
            • GU (other than kidney, bladder, and prostate)  
            • Biliary tract                                       |
| Unfavorable| Any site not listed as favorable in above                                     |
| T1 and T2  | Tumor confined to anatomical site of origin (T1)  
            Tumor extension and/or fixation to surrounding tissue (T2) |
| a and b    | Tumor ≤ 5 cm in diameter (a)  
            Tumor > 5 cm in diameter (b)                                    |
| N0 and N1  | Presence (N1) or absence (N0) of regional LN                               |
| NX         | Unable to assess regional lymph node status                                 |
| M0 and M1  | Presence (M1) or absence (M0) of metastasis                                |

TNM Staging Classification

<table>
<thead>
<tr>
<th>Stage</th>
<th>Primary Site</th>
<th>T Stage</th>
<th>Tumor Size</th>
<th>Regional LN</th>
<th>Distant Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Favorable</td>
<td>1 or 2</td>
<td>Any</td>
<td>N0, N1, NX</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>Unfavorable</td>
<td>1 or 2</td>
<td>a, ≤ 5 cm</td>
<td>N0, NX</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>Unfavorable</td>
<td>1 or 2</td>
<td>a, ≤ 5 cm</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>b, &gt; 5 cm</td>
<td>N0, N1, NX</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Any</td>
<td>1 or 2</td>
<td>Any</td>
<td>N0, N1, NX</td>
<td>M1</td>
</tr>
</tbody>
</table>

IRS Clinical Group Classification

- Group I
  - Localized disease
  - GTR
- Group II
  - GTR with evidence of regional spread
  - Microscopically positive margins or involved nodes (completely excised)
**IRS Clinical Group Classification**

- **Group III**
  - Incomplete resection with gross residual disease
  - Biopsy only

- **Group IV**
  - Distant metastases

**COG Risk Stratification**

<table>
<thead>
<tr>
<th></th>
<th>Low Risk</th>
<th>Intermediate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metastases</strong></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td>Embryonal</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td>Group I or II</td>
<td>Any stage Group III</td>
<td>Group IV</td>
</tr>
<tr>
<td></td>
<td>Group I, II, or III</td>
<td>Stage 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Group 2 or 3</td>
<td>Stage 2 or 3 Embryonal</td>
<td>Stage 2 or 3</td>
</tr>
<tr>
<td><strong>Clinical Group</strong></td>
<td>Stage 1</td>
<td>Group I, II, or III</td>
<td>Group IV</td>
</tr>
<tr>
<td></td>
<td>Stage 2 or 3</td>
<td>Group III</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alveolar</td>
<td>Group T, II, or III</td>
<td></td>
</tr>
</tbody>
</table>

**Cytogenetics**

<table>
<thead>
<tr>
<th><strong>Alveolar</strong></th>
<th><strong>Embryonal</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>t(2;13)(q35;q14)</td>
<td>Specific translocations not identified</td>
</tr>
<tr>
<td>PAX3-FKHR</td>
<td>LOH at chromosome 11p15</td>
</tr>
<tr>
<td>55% of cases</td>
<td>80% of cases</td>
</tr>
<tr>
<td>Worse prognosis</td>
<td>Common to see loss or gain of chromosomes</td>
</tr>
<tr>
<td>23% of cases</td>
<td>50% gain of chromosome 8</td>
</tr>
</tbody>
</table>

**Embryonal**

- Specific translocations not identified
- LOH at chromosome 11p15
- Common to see loss or gain of chromosomes
- 50% gain of chromosome 8

**Historical Perspective**

**Low- and Intermediate-Risk Disease**

**Where it all began…**

- Initially described by Weber in 1821 yet….
- Definitive publication by Stout in 1946

**The Beginning**

- IRSG
  - Conducted the largest series of clinical trials for patients prior to merger of the pediatric cooperative groups

- Looked at
  - Chemotherapy combinations
  - Methods of delivering XRT
  - Degree/timing of surgical resection

- 1972-1997
  - Enrolled 4292 patients
### Historical Perspective of RMS Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>ERA</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRS- I</td>
<td>1972-1978</td>
</tr>
<tr>
<td>IRS- II</td>
<td>1978-1984</td>
</tr>
<tr>
<td>IRS- III</td>
<td>1984-1991</td>
</tr>
<tr>
<td>IRS- IV (HR only)</td>
<td>1987-1991</td>
</tr>
<tr>
<td>IRS- IV</td>
<td>1991-1997</td>
</tr>
</tbody>
</table>

Raney, et al., 2001

### And the Studies Show…

<table>
<thead>
<tr>
<th>Modality</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>• May not be optimal for all patients (i.e., eye, bladder, vagina)</td>
</tr>
<tr>
<td></td>
<td>• Patients who are older at diagnosis are more likely to have a</td>
</tr>
<tr>
<td></td>
<td>greater degree of regional LN involvement</td>
</tr>
<tr>
<td></td>
<td>• Best prognosis if:</td>
</tr>
<tr>
<td></td>
<td>- Localized/GTR</td>
</tr>
<tr>
<td></td>
<td>- Tumor free margins</td>
</tr>
<tr>
<td>XRT</td>
<td>• IRS-III &amp; IV demonstrated improved outcomes in patients receiving</td>
</tr>
<tr>
<td></td>
<td>intensified therapy</td>
</tr>
<tr>
<td></td>
<td>• No benefit for</td>
</tr>
<tr>
<td></td>
<td>- Completely resected/localized tumors</td>
</tr>
<tr>
<td></td>
<td>- Hyperfractionated delivery</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>• VAC vs. VAI or VIE – no difference in outcome BUT</td>
</tr>
<tr>
<td></td>
<td>↑ toxicity with VAI and VIE</td>
</tr>
<tr>
<td></td>
<td>• VAC = Gold Standard for LR/IR patients</td>
</tr>
<tr>
<td></td>
<td>• IE and VADRIAC added to VAC backbone for HR patients</td>
</tr>
</tbody>
</table>

Raney, et al., 2001

### Relapse

- 30% of patients will experience relapse
  - 80% = “unfavorable” prognosis
  - 10% overall survival at 5 years
  - 20% = “favorable” prognosis
  - Botryoid or Stage I, Group I embryonal histology
  - 50% overall survival at 5 years

Pappo, et al., 1999

### The Problem Remains

Unchanged or poor survival in IR, HR, and relapsed patients despite incorporation of new chemotherapeutic agents

### The Answer Lies on the Horizon

- Refining risk stratification based on biology-based metrics
- Novel targeted therapies
- Clinical trials
High-Risk RMS

- High-Risk = metastatic disease at presentation
  - Stage IV
  - Clinical Group IV
- Incidence
  - 16% of all cases of RMS
- Survival
  - 5-year survival: 20-30%
  - 3-year EFS = <20% in patients >10 yrs of age

ARST08P1
A Pilot Study to Evaluate Novel Agents (Temozolomide (TMZ) and Cixutumumab [IMC-A12, Anti-IGF-IR Monoclonal Antibody]) in Combination with Intensive Multi-Agent Interval Compressed Therapy for Patients with High-Risk Rhabdomyosarcoma

ARST08P1: High-Risk RMS

**Purpose**
Evaluate the addition of novel agents to intensive chemotherapy backbone

**Pilot Studies**

<table>
<thead>
<tr>
<th>Pilot</th>
<th>Study Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pilot 1</td>
<td>Addition of IGF-IR inhibitor, IMC-A12</td>
</tr>
<tr>
<td>Pilot 2</td>
<td>Addition of TMZ</td>
</tr>
<tr>
<td>Pilot 3</td>
<td>Addition of IMC-A12 and TMZ</td>
</tr>
</tbody>
</table>

ARST08P1: Objectives

**Primary objectives to determine the feasibility of:**
- Administering IMC-A12 in combination with a multi-agent intensive chemotherapy regimen
- Adding TMZ to VI cycles and to assess immediate and short-term SEs of delivery of concurrent VIT with XRT

**Secondary objectives to:**
- Estimate the response rate for IMC-A12 and/or TMZ plus VI
- Obtain efficacy data for IMC-A12 and/or TMZ in combination with an interval compressed chemotherapy regimen
- Determine effectiveness of detecting metastatic disease and response with FDG PET compared to standard imaging
- Assess changes in serum levels of IGF-I, IGF-II, IGF-BP3 as biomarkers of IGF-IR inhibition

ARST08P1: Eligibility

- Newly diagnosed, biopsy proven metastatic RMS or ectomesenchymoma
- Less than 50 years old
- Must enroll on biology study COG-D9902
- No prior chemotherapy or radiation therapy
  - Steroids and emergent XRT acceptable
- **Not Eligible**
  - Patients with uncontrolled infections

Patients with known Type I or II diabetes mellitus are NOT eligible for Pilot 1 or 3.

ARST08P1: Chemotherapy Backbone

- Based on previous High-Risk RMS study, ARST0431
- Incorporates all agents known to be active in RMS
  - Vincristine, irinotecan, doxorubicin, CPM, ifosfamide, etoposide
- VADRIAC and IE administered in an interval compression model

Rhabdomyosarcoma: Progress and Challenges in Clinical Trials
ARST08P1: Local Control

- XRT
  - XRT to primary and metastatic sites at Week 20
- Surgery
  - Generally biopsy only
  - Second look surgery
    - Possible for patients with stable or resolving metastatic disease
    - Must aim for complete resection without significant loss of function or cosmesis
    - Timing: After Week 19 evaluations & before starting Week 20 chemotherapy and XRT

IMC-A12

- Cixutumumab
- Fully humanized IgG1 monoclonal antibody targeting IGF-IR
- IGF-IR
  - Transmembrane receptor kinase
  - Promotes tissue growth by mediating the effects of IGF-I and IGF-II ligands
  - Ligand binding results in cellular proliferation and inhibition of apoptosis

IMC-A12 (continued)

- Inhibits ligand binding to IGF-IR resulting in
  - Decreased proliferation of cancer cell lines
  - Suppressed downstream signaling of P13k and MAPK pathways
  - Suppressed tumor growth

IMC-A12 – Phase I Trials

- Phase I adult trial
  - MTD not reached
  - Most significant adverse event: HYPERGLYCEMIA
  - Recommended adult dose: 6mg/kg weekly
- Phase I pediatric trial (ADVL0712)
  - Children with refractory solid tumors
  - One DLT at 6mg/kg and none at 9mg/kg
  - Grade 2 or higher toxicities
    - Anemia, leukopenia, lymphopenia, neutropenia, opportunistic infection, elevated LFTs, hyperglycemia
  - Recommended Phase II dose: 9mg/kg weekly

IMC-A12: Administration

- IV infusion over 1 hour (infusion rate not to exceed 25mg/min via PIV or central line)
- Dilutions based on age and dose
- Administer with an in-line protein-sparing filter
- Flush following infusion with 0.9% NaCl
- Pre-medication NOT required unless previous history of reaction
- Administer after other chemotherapy is given
- Hold during XRT

IMC-A12: Toxicities

- Likely toxicities (>20% of patients)
  - Fatigue
  - Hyperglycemia
- Less likely (<20% of patients)
  - Infusion-related reactions
  - Allergic reactions
  - Anaphylactic reactions (<3%)

Rhabdomyosarcoma: Progress and Challenges in Clinical Trials
Hyperglycemia

- Based on random, non-fasting glucose levels
- Grade 1 or 2
  - Consider Endocrine consult
  - No changes in IMC-A12 dosing
  - Initiate insulin or oral diabetic agent
  - Hold IMC-A12 until resolves to ≤ Grade 2 without glycosuria
  - Resume at same dose IF
    - Asymptomatic AND serum glucose consistently remains <250mg/dL without glycosuria
    - May continue to receive concomitant insulin or oral diabetic agent

- Grade 3 (blood glucose >250-500mg/dL or urine glucose >0.1g/dL)
  - Consider Endocrine consult
  - No changes in IMC-A12 dosing

- Grade 3 (blood glucose >250-500mg/dL or urine glucose >0.1g/dL)
  - Based on random, non-fasting glucose levels
  - Grade 1 or 2
    - Consider Endocrine consult
    - No changes in IMC-A12 dosing
    - Initiate insulin or oral diabetic agent
    - Hold IMC-A12 until resolves to ≤ Grade 2 without glycosuria
    - Resume at same dose IF
      - Asymptomatic AND serum glucose consistently remains <250mg/dL without glycosuria
      - May continue to receive concomitant insulin or oral diabetic agent

- Grade 3
  - Initiate insulin or oral diabetic agent
  - Hold IMC-A12 until resolves to ≤ Grade 2
  - Resume IMC-A12 with one dose reduction IF
    - Patient is asymptomatic and serum glucose is consistently <250mg/dL without glycosuria
    - May continue to receive concomitant insulin or oral diabetic agent

Goal of insulin/oral diabetic agents = fasting blood sugars <126mg/dL and HgbA1C <8%.

Hyperglycemia (continued)

- Grade 4
  - Initiate insulin therapy as indicated
  - Hold IMC-A12 until resolves to ≤ Grade 2
  - Resume IMC-A12 with one dose reduction IF
    - Patient is asymptomatic and serum glucose is consistently <250mg/dL without glycosuria
    - May continue to receive concomitant insulin or oral diabetic agent

Allergic Reactions

<table>
<thead>
<tr>
<th>Grade</th>
<th>Symptom</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Transient flushing or rash, drug fever &lt;38°C (&lt;100.4 F)</td>
<td>Slow infusion rate by 50%</td>
</tr>
<tr>
<td>2</td>
<td>Rash, flushing, urticaria, dyspnea, drug fever &lt;38°C (&lt;100.4 F)</td>
<td>Stop infusion&lt;br&gt;<strong>Symptom control as needed:</strong>&lt;br&gt;- diphenhydramine&lt;br&gt;- acetaminophen&lt;br&gt;- oxygen&lt;br&gt;- Resume infusion at 50% when reaction decreased to ≤ grade 1&lt;br&gt;- Pre-mEDIATE with diphenhydramine for subsequent doses&lt;br&gt;- If grade 1-2 reactions reoccur add IV dexamethasone as premed</td>
</tr>
</tbody>
</table>

Goal of insulin/oral diabetic agents = fasting blood sugars <126mg/dL and HgbA1C <8%.

Allergic Reactions

<table>
<thead>
<tr>
<th>Grade</th>
<th>Symptom</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Bronchospasm with or without urticaria&lt;br&gt; Allergy-related edema/angioedema&lt;br&gt; Hypotension</td>
<td>Stop infusion&lt;br&gt;<strong>Medicate as indicated:</strong>&lt;br&gt;- dexamethasone IV(0.2 mg/kg /max 10 mg)&lt;br&gt;- bronchodilators&lt;br&gt;- other supportive care medications&lt;br&gt;- Consider hospitalization for observation&lt;br&gt;- Discontinue IMC-A12</td>
</tr>
<tr>
<td>4</td>
<td>Anaphylaxis</td>
<td>Stop infusion&lt;br&gt;<strong>Medicate as indicated:</strong>&lt;br&gt;- dexamethasone IV(0.2 mg/kg /max 10 mg)&lt;br&gt;- epinephrine and bronchodilators&lt;br&gt;- other supportive care medications&lt;br&gt;- Consider hospitalization for observation&lt;br&gt;- Discontinue IMC-A12</td>
</tr>
</tbody>
</table>

Non-Hematologic Toxicities

- No dose modifications for the following
  - Diarrhea
  - Anorexia
  - Weight loss
  - Dehydration
  - Nausea/Vomiting
  - Mucositis/Stomatitis
  - Fever or febrile neutropenia

Temozolomide

- Second generation imidazotetrazine prodrug
  - Undergoes spontaneous hydrolysis to the active metabolite, MTIC
  - Methylates DNA at O6 guanine and other sites
  - Found to have synergy with irinotecan
  - Activity of irinotecan can be improved with pre-treatment with temozolomide
  - Reaches peak concentration in 1 hour

Danson & Middleton, 2001
Temozolomide (continued)

- Irinotecan, temozolomide, and vincristine initially tested as 2-week regimen
- MSKCC studied temozolomide and irinotecan
  - Administered daily x5
  - Found to be feasible with limited toxicities
    - GI
    - Myelosuppression

Kushner, Kramer, Modak, & Cheung, 2006

Temozolomide: Administration

- Administer on empty stomach
  - Food decreases rate and extent of absorption
- If cannot swallow capsules
  - May be formulated by pharmacist into suspension
  - May mix contents of capsule with apple sauce or apple juice
    - All mixing should be done with disposable containers and utensils

Temozolomide: Prescribing/Dispensing

- Only dispense what is needed for each course
  - Clearly indicate number of capsules to be taken
- Clearly indicate which days temozolomide will/will not be taken
- Each strength capsule will be dispensed in a separate, dark container

Temozolomide: Side Effects

Common
- N&V
- Anorexia
- Constipation
- Myelosuppression
- Alopecia
- Diarrhea
- Mucositis
- Lethargy
- Rash/Itching
- Hepatotoxicity
- Abdominal pain
- Peripheral edema
- Urinary frequency/UTI

Less Common

Temozolomide: Prescribing/Dispensing

- Only dispense what is needed for each course
  - Clearly indicate number of capsules to be taken
- Clearly indicate which days temozolomide will/will not be taken
- Each strength capsule will be dispensed in a separate, dark container

ARST08P1: Study Status

Progress
- Opened January 2010
- Exceeding accrual estimates
- No unexpected toxicities despite chemotherapy backbone
- Eligibility expanded to include patients with metastatic embryonal RMS < 10 years of age

Nursing Considerations (Nutrition/Skin)

- Nutrition
  - Support recommended for ≥10% weight loss
  - GH not allowed
  - Avoid megesterol
- Mucositis
  - Patient education re: oral hygiene
  - Dental consult — especially if head/neck XRT
  - Recommend removal of braces
- Skin
  - Painless/Reversible nail sloughing with compressed regimen
  - Painful inflammation/desquamation of the palms/soles
    - If occurs ↑ therapy interval to 21 days; reattempt 14-day cycle
Nursing Considerations (Diarrhea)

▪ If the following occurs during 1st course of VI

   Grade 3 or 4
   • Colitis
   • Diarrhea
   • Vomiting
   • Dehydration
   • Weight loss
   • Abdominal pain

   Begin cefixime/cefpodoxime 5 days prior to starting 2nd course of chemotherapy (if not feasible, minimum 1 day prior)
   Continue PO antibiotics through Day 21

   Management of both early and late diarrhea outlined in Supportive Care Guidelines (ARST08P1, Appendix X)

Nursing Considerations (Infection)

▪ Hematopoietic growth factors
  • Required for interval compression after VADRIAC and IE cycles
  • Recommended after VAC (not after VI or VIT)
  • Begin a full 24 hours following last dose of chemotherapy
  • Subcutaneous preferred route

▪ PCP prophylaxis
  • Bactrim™ (TMP 2.5mg/kg/dose; max 160mg)
  • PO BID three consecutive days per week
  • Switch to pentamidine during chemoradiotherapy when receiving temozolomide

Understanding Late Effects in RMS

▪ Broken down into two groups
  ♦ Those caused by
    1. Systemic therapy
    2. Local control therapy
  ♦ Location of tumor is KEY

Late Effects of Treatment

Late Effects (Infertility)

▪ Related to local control and/or systemic therapy
  1. Alkylating agents (systemic therapy)
     • Ifosfamide
     • Cyclophosphamide
  2. XRT (local therapy)
     • Move testes or ovaries out of XRT field when possible
  3. Surgery (local therapy)
  4. Risk greater for boys than girls
     • When feasible
       1. Sperm banking
       2. Egg harvesting

Late Effects (Bladder Dysfunction)

▪ Related to local control and/or systemic therapy
  1. Chemotherapy (systemic)
  2. XRT and surgery (local)
  3. Toxicity
     1. Bladder fibrosis
     2. Hemorrhagic cystitis
     3. Dysfunctional voiding
  4. ~50% of patients will have symptoms
     1. Dribbling
     2. Enuresis
  5. No predictors of the severity of the symptoms
Late Effects (Head and Neck)

- Related to local control with XRT
  - Direct result of inability to obtain complete surgical resection due to location of tumor
- Common late effects
  - Cataracts
  - Chronic sinus infections
  - Asymmetric facial growth
  - Growth failure due to pituitary damage
  - Complex and multiple dental abnormalities

Late Effects (SMN)

- Chemotherapy
  - Secondary leukemia
    - Alkylating agents (CPM & IFOS)
    - Topoisomerase II inhibitors (ETOP & DOXO)
  - Bladder cancer (CPM)
- XRT
  - Skin
  - Bladder
  - Sarcoma
  - CNS (benign or malignant)
- Underlying genetic disorders may predispose patients to developing a SMN

References


