Maintenance Chemotherapy In Childhood Rhabdomyosarcoma

A.Eghbali MD

Pediatric Hematologist & oncologist
Iran University of Medical Sciences


بنام خداوند جان و خرد

Maintenance Therapy In Childhood RMS

Maintenance therapy in childhood Rhabdomyosarcoma is an emerging strategy aimed at Improving long-term outcomes by Reducing the Risk of Relapse after initial successful treatment .

Maintenance Therapy In Childhood RMS

Maintenance therapy in pediatric (RMS) refers to a prolonged, less intensive phase of chemotherapy administered after the initial multimodal treatment,

- The goal is:
  - Target any residual microscopic disease
  - Sustain remission
  - Reduce the risk of relapse

Role of Maintenance Therapy in Childhood Rhabdomyosarcoma:

01

Reducing Relapse Risk

RMS is aggressive and prone to relapse
even after initial remission.

Maintenance therapy aims to
eradicate microscopic residual disease that may cause relapse.

02

Improving Overall Survival

Studies have suggested that adding maintenance chemotherapy can improve survival rates in high-risk patients.

For example, trials like the EpSSG RMS 2005 showed that maintenance therapy with vinorelbine and low-dose cyclophosphamide improved event-free survival in patients with high-risk RMS.

03

Targeted Low-Intensity Treatment

Maintenance regimens usually consist of
less intensive chemotherapy
(oral cyclophosphamide, vinorelbine)
that is easier to tolerate,
minimizing side effects compared to initial induction therapy.

04

Patient Selection

Generally considered for patients with high-risk or metastatic RMS who have responded to initial therapy.

The role in low- or intermediate-risk RMS is less clear and not routinely used.

- **Maintenance therapy is beneficial particularly in intermediate- or high-risk patients:**

  - Children with nonmetastatic / incompletely resected embryonal RMS at unfavorable sites

    - ✓ Especially if age ≥10 years or tumor >5 cm

  - Embryonal RMS with nodal involvement

  - Alveolar RMS without nodal involvement

05

Ongoing Research

Maintenance therapy protocols are still evolving,
with ongoing clinical trials assessing the best agents,duration,
and patient subsets that benefit most.

Ongoing Research

Ongoing Research

The European pediatric Soft Tissue Sarcoma Study Group (EpSSG) conducted the **RMS 2005 trial**, a pivotal phase III study that evaluated the efficacy of maintenance chemotherapy in this context.

Ongoing Research (RMS 2005 Trial)

RMS 2005 Trial:

Study Design: This multicenter, open-label,randomized trial involved 371 patients aged 6 months to 21 years with high-risk RMS.

Patients in remission after standard therapy (which included surgery, radiotherapy, and nine cycles of chemotherapy with ifosfamide, vincristine, dactinomycin, and/or doxorubicin) were randomly assigned to either continue with maintenance therapy or to stop treatment.

Ongoing Research (RMS 2005 Trial)

RMS 2005 Trial
Maintenance Regimen:

The maintenance therapy consisted of six 4-week cycles of intravenous vinorelbine (25 mg/m^2 on days 1, 8, and 15) and oral cyclophosphamide (25 mg/m^2 daily for 28 days).

Ongoing Research (RMS 2005 Trial)

RMS 2005 Trial Outcomes:

Overall Survival (OS): The 5-year OS rate was 86.5% in the maintenance group compared to 73.7% in the control group (p = 0.0097).

Disease-Free Survival (DFS): The 5-year DFS rate was 77.6% in the maintenance group versus 69.8% in the control group (p = 0.061).

Ongoing Research (RMS 2005 Trial)

RMS 2005 Trial
Toxicity:

The maintenance regimen was generally well-tolerated.

Common grade 3–4 adverse events included Neutropenia (82%), leukopenia (75%), and infections (31%). Notably, there were no reports of cardiac, hepatic, gastrointestinal, or renal toxicity.

Ongoing Research (RMS 2005 Trial)

Clinical Implications

Standard of Care: The RMS 2005 trial's findings have established maintenance chemotherapy as a new standard of care for high-risk RMS patients in Europe.

Ongoing Research: Further studies are needed to optimize maintenance therapy protocols,
including the duration of treatment and
the potential incorporation of novel agents.

Ongoing Research (RMS 2005 Trial)

Future Directions :

Combination Therapies: Exploring the addition of targeted therapies or immunotherapies to maintenance regimens may further improve outcomes.

Biomarker Development: Identifying biomarkers to predict which patients are most likely to benefit from maintenance therapy could lead to more personalized treatment approaches.

Ongoing Research (RMS 2005 Trial)

In conclusion

maintenance therapy with
vinorelbine and cyclophosphamide represents
a significant advancement in the treatment of
high-risk childhood rhabdomyosarcoma,
offering improved survival rates with manageable toxicity.

Ongoing and Recent Clinical Trials

UCSF Rhabdomyosarcoma Trial (USA)

This Phase III study is evaluating the safety and efficacy of adding vinorelbine to the VAC regimen, followed by maintenance therapy with vinorelbine and oral cyclophosphamide.

The trial started in September 2021 and is expected to conclude around September 2027.

Observational and Retrospective Studies

Observational and Retrospective Studies

Sun Yat-sen University Cancer Center Study (China)

A recent retrospective study from Sun Yat-sen University Cancer Center in China analyzed data from 459 pediatric RMS patients diagnosed between 2011 and 2020.

Of these, 57 patients received maintenance therapy with oral vinorelbine (25–40 mg/m² on days 1, 8, and 15) and oral cyclophosphamide (25–50 mg/m² daily for 48 weeks).

Observational and Retrospective Studies

Sun Yat-sen University Cancer Center Study (China)

Results:

A total of 57 patients who underwent MMT were included in the analysis.

The median follow-up time was 27.8 (range: 2.9–117.5) months.

From MMT to the end of follow-up, the 3-year PFS and OS rates were 40.6% ± 6.8% and 58.3% ± 7.2%, respectively.

Observational and Retrospective Studies

Sun Yat-sen University Cancer Center Study (China)

Conclusion:

The MMT strategy significantly improved patient outcomes and may be an effective treatment for high-risk and relapsed patients.

Observational and Retrospective Studies

Phase II Study by SFCE (France)

This study assessed the combination of intravenous vinorelbine and continuous low-dose oral cyclophosphamide in children and young adults with Relapsed or Refractory solid tumors, including RMS.

The regimen showed a 36% overall response rate in RMS patients, with manageable toxicity.

Observational and Retrospective Studies

CWS2002P and CWS2007 HR Trials (Germany)

These studies by the Cooperative Weichteilsarkom Studiengruppe (CWS) explored maintenance chemotherapy (MC) in high-risk localized RMS.

The CWS2002P trial showed improved event-free survival in patients who received maintenance therapy.

However, the CWS2007 HR trial did not demonstrate a significant difference in survival outcomes between maintenance therapy and stopping treatment.

Observational and Retrospective Studies

CWS2002P and CWS2007 HR Trials (Germany)

These studies collectively *highlight the potential benefits of maintenance therapy in improving survival outcomes for high-risk childhood RMS patients.*

While the combination of vinorelbine and cyclophosphamide has shown promise, ongoing trials and further research are essential to optimize treatment protocols and confirm long-term efficacy.

Observational and Retrospective Studies

ARST2031 Trial Details (Based on ASCO Abstract)

This randomized Phase III study evaluates whether adding vinorelbine to standard therapy, followed by maintenance, improves (EFS) in (HR-RMS) patients:

Observational and Retrospective Studies

ARST2031 Trial Details (Based on ASCO Abstract)

Objective: Compare EFS between:

Arm A (VAC + VINO-CPO):

Standard vincristine, dactinomycin, cyclophosphamide (VAC) followed by maintenance with vinorelbine and oral cyclophosphamide (VINO-CPO)

Arm B (VINO-AC + VINO-CPO):

Modified induction—vinorelbine, dactinomycin, cyclophosphamide (VINO-AC)—plus the same VINO-CPO maintenance

Observational and Retrospective Studies

ARST2031 Trial Details (Based on ASCO Abstract)

Design & Enrollment:

- Activated: September 13, 2021
- Target accrual: ~100 patients (≈50 per arm)
- Safety run-in: The first 8 patients on VINO-AC are assessed for safety/feasibility before full randomization.

Observational and Retrospective Studies

ARST2031 Trial Details (Based on ASCO Abstract)

Summary

Full-text publication of ARST2031 results is not publicly available yet.

The abstract in Journal of Clinical Oncology (JCO 2022) provides essential info on trial design, regimen, endpoints, and statistical planning.
Additional details on eligibility, study arms, and objectives are accessible via clinical trial registries and research institution pages.

Latest Trial: RMS13 (Presented at ASCO 2024)

Latest Trial: RMS13 (Presented at ASCO 2024)

The most recent trial in this category is
the RMS13 Phase II study,
reported at the 2024 ASCO meeting by Pappo et al.

Patient population: Children and adolescents (under 22 years) with intermediate-risk RMS—embryonal, botryoid, spindle, or alveolar/unclassified

Latest Trial: RMS13 (Presented at ASCO 2024)

RMS.

Maintenance regimen:

After 14 cycles of standard VAC chemotherapy, patients received four cycles combining low-dose cyclophosphamide, bevacizumab, and sorafenib.

Latest Trial: RMS13 (Presented at ASCO 2024)

Outcomes:

- 5-year (OS): 75.1%
- 5-year (EFS): 67.5%
- Efficacy was constrained by tolerability about 25% of patients were unable to complete maintenance therapy.

This trial is the latest known testing of a maintenance protocol in pediatric RMS.

Latest Trial: RMS13 (Presented at ASCO 2024)

The RMS13 study represents the latest completed investigation into maintenance therapy in childhood RMS, extending maintenance beyond traditional chemotherapy by incorporating targeted agents but faced challenges with tolerability.

The ARST2031 trial remains the most promising upcoming data source for maintenance therapy in high-risk RMS.

Thanks
For
Your attention