Approach to chemotherapy for high-risk, stage 1, non-seminomatous, germ cell testicular tumors

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SUMMARY

The 111 trial[1] published in European Urology this year examines whether single-cycle Bleomycin, etoposide, platinum (BEP) with etoposide 500 mg/m^2 is comparable to two cycles of BEP with etoposide 360 mg/m^2, with better toxicity profile; and whether it should be preferred over surveillance for T1 high risk testicular nonseminomatous germ cell testiculars (NSGCTs) and Stage IB nonmetastatic tumors to avoid recurrence. It was a single-arm trial using historical data as control. Patients >16 years age and fit for chemotherapy were included in the study. Patients with previous malignancy, previous chemotherapy, serious comorbidity, neuropathy, pulmonary fibrosis, and impaired liver functions were excluded. Single-cycle chemotherapy with neutropenic sepsis prophylaxis (fluoroquinolones + granulocyte colony-stimulating factors[G-CSF] was administered 6-8 weeks after radical inguinal orchiectomy and followed up with clinical examination, tumor markers, imaging, and toxicity assessment for up to 2 years. A total of 246 patients were accrued, and 228 patients completed the follow-up of 2 years. The trial was powered to exclude a 2-year malignant recurrence rate of 5% with 80% power and 5% alpha. At each recurrence, statistical analysis was performed to keep a check on whether this <5% recurrence target will be achieved with respect to historical controls while preserving the final alpha of 5% and power of 80%. An interim analysis was performed at the completion of 2 years follow-up for 157 patients. Any histological, multiple-site or biochemical recurrence of NSGCT was labeled as malignant recurrence. Single-site recurrence, differentiated teratoma, and non-malignant recurrence were labeled as benign recurrence.

There were a total of four malignant (NSGCT) and three benign (Teratoma) recurrences. Whereas three malignant recurrences were successfully treated with retroperitoneal lymph node dissection and chemotherapy, one patient succumbed to fulminant disease, 9 months after accrual. The long-term toxicity of chemotherapy was low making it an acceptable option. No patient needed to discontinue the chemotherapy due to neutropenia or other serious side effects. The total (benign + malignant) recurrences were <5%. It was concluded that single-cycle high-dose etoposide was as good as two-cycles of low-dose etoposide in preventing recurrence after Stage I high-risk NSGCT and associated with acceptable toxicity, thus making it a viable option in the treatment of such patients outside a clinical trial setting.

COMMENTS

Standard treatment for Stage I NSGCT post radical inguinal orchiectomy is surveillance with one or two cycles of chemotherapy as a shared decision-making process as per the latest AUA guidelines, whereas EAU 2020 recognizes the potential of single cycle in reducing the duration of treatment while maintaining its efficacy.[2,3]

Chemotherapy duration and the number of cycles advocated in the current guidelines seem to be adequate in advanced cancers but for a subset of patients with Stage I high-risk tumors, two cycles of BEP may be "overkill." Several small-scale studies have tried shortening the duration of chemotherapy to single cycle.[4,5] Active surveillance maybe "underkill" with a 50% recurrence rate requiring three cycles of chemotherapy with BEP with significant toxicity. Smaller sample sizes and heterogeneous protocols of these studies prevented single cycle chemotherapy from being considered a standard treatment.

This study provided us with evidence that single-cycle chemotherapy in selected patients may be comparable to two-cycle chemotherapy. The study design could have been better had it included a control group of surveillance only and the third arm of standard two-cycle chemotherapy. Furthermore, neutropenic sepsis prophylaxis with G-CSF and antibiotic as a routine appears to be against the rational use of antibiotics and probably will increase the cost of treatment if compared to selective treatment. A 32% rate of neutropenia and 40% rate of leukopenia with 6.8% severe febrile neutropenia in acute settings also raise questions

on the efficacy of this prophylaxis. The effects on fertility and long-term follow-up of this study remain to be seen. It is important to know that a noninferiority trial would have required accrual of 1110 patients, which is difficult to achieve for a subset this specific.

Due to poor adherence and follow-up in India, this regimen may be a useful option to ensure compliance and give comparable long-term outcomes with less toxicity. Some of the questions that may intrigue a researcher are, whether the duration of chemotherapy for non-Stage I NSGCT may also be shortened by increasing the dose of a single agent, or whether this regimen will work on extragonadal NSGCTs. In the current scenario of COVID-19, larger studies will be difficult to perform and probably we will have to wait to see newer studies that address these issues.

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