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NCCN Guidelines Panel: Testicular Cancer

I am requesting the NCCN Guidelines panel to consider review of data for two specific proposed changes:

- Specific Indication:
  1) Treatment for good-risk metastatic testicular cancer.
  2) Post-chemotherapy management after achieving a complete remission.

- Specific Changes Recommended:
  1) BEP x 3 should be the **preferred** option for patients with good-risk metastatic disease.
  2) Surveillance should be the **preferred** option for post-chemotherapy management following a complete remission.

- Statement of whether the submitted is or is not FDA approved for that indication:
  Not applicable.

- Rationale for recommended change:
  Although the NCCN Guidelines is the worldwide standard, most other international guidelines and pathways lists BEP x 3 as the preferred option.

- Citation of literature support:
  See text.

BEP x 3 vs. EP x 4 for Good-risk Metastatic Disease

All phase III studies that have been performed with and without bleomycin had numerical superiority for the bleomycin arm. With the usual > 90% cure rate, there is no statistical superiority. The most robust study was published by Culine and French colleagues (1). This study randomized 251 patients. The progression-free survival of 91% vs. 86% favor BEP x 3 and the 4 year survival of 96% vs. 92% also favored BEP with 5 vs. 10 deaths ($p = 0.14$), again favoring the bleomycin arm. As was true with virtually all published studies with BEP x 3 in good-risk disease, there were no deaths from bleomycin.

A recent commentary by investigators at Tufts concluded "there is sufficient basis to reshape the National Guidelines in good-risk disease towards a preference of 3 BEP over 4 EP" (2). They cite numerous studies supporting this conclusion.

Although there is increased Raynaud's with bleomycin, there is no clear evidence of increased early or late vascular toxicity. The most toxic drug for acute and late toxicity, in my opinion, is cisplatin which causes cumulative anorexia, nausea, peripheral neuropathy and ototoxicity. The latter was quantitated in a multi-institutional study looking at late complications of cisplatin chemotherapy. Every 100 mg/M^2 increase in cumulative cisplatin resulted in a 2.5 dB decrease in hearing thresholds ($p = 0.0049$), and this was associated with increased tinnitus (3).

Surveillance vs. RPLND in Metastatic Testicular Achieving a Complete Remission

There will never be a randomized study testing these two concepts. At Indiana University, we have never done a post-chemo RPLND in patients who achieve a complete remission which we define as lymph nodes < 1 cm in maximal transverse diameter. We have published our data with median followup of over 15 years (4) with retrospective analysis of 141 patients. Twelve of these 141 patients (9%) relapsed and 8 of the 12 are currently NED with further therapy. Only 6 relapses out of 141 patients occurred in the retroperitoneum and 4 of those 6 are currently disease-free. Among the 12 relapses, 5 of them were late relapses and all are currently NED with

subsequent surgery. No matter how effective any therapy is in any individual setting, including surgery or chemotherapy, there will never be a situation where there are zero relapses after achieving a complete remission. This is the largest published data set looking at observation in this clinical setting. A very large number of patients would have to undergo a post-chemo RPLND to have any theoretical advantage. This is why we feel that surveillance after achieving a complete remission in metastatic testicular cancer is the preferred option and we would like to see this JCO reference (4) listed in the NCCN Guidelines.

References:

1. Culine S, Kerbrat B, Kramer A, et al.: Genitourinary Group of the French Federation of Cancer Centers. Refining the Optimal Chemotherapy Regimen for Good-risk Metastatic Non-seminomatous Germ Cell Tumors: A Randomized Trial of the Genitourinary Group of the French Federation of Cancer Centers. Ann Oncol 18:917-924, 2007.
2. Fein DE, Paulus JK, and Matthews Paul: Reassessment of 4-Cycle Etoposide and Cisplatin as the Standard of Care for Good-risk Metastatic Germ Cell Tumors. JAMA Onc 4:1661-1662, 2018.
3. Frisina RD, Wheeler HE, Fossa SD, et al.: Comprehensive Audiometric Analysis of Hearing Impairment and Tinnitus after Cisplatin-based Chemotherapy in Survivors of Adult-Onset Cancer. J Clin Onc 34:2712-2720, 2016.
4. Ehrlich Y, Brames MJ, Beck SDW, Foster, RS, and Einhorn LH: Long-term Followup of Cisplatin Combination Chemotherapy with Disseminated Non-seminomatous Germ Cell Tumor: Is a Post-chemotherapy Retroperitoneal Lymph Node Dissection Needed Following Complete Remission? J Clin Onc 28:531-536, 2010.

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