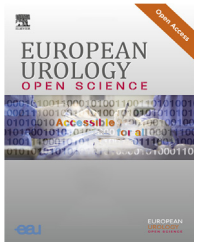
EUROPEAN UROLOGY OPEN SCIENCE 49 (2023) 69–70

available at www.sciencedirect.com
journal homepage: www.eu-openscience.europeanurology.com



European Association of Urology

Open to Debate: Con

Stage II Seminoma: Why Chemotherapy Should Remain a Standard

Natacha Naoun *, *Alice Bernard-Tessier*, *Karim Fizazi*

Department of Cancer Medicine, Institut Gustave Roussy, University of Paris Saclay, Villejuif, France

Article info

Article history:
Accepted June 28, 2022

Associate Editor:
M. Carmen Mir

Abstract

Chemotherapy (three cycles of bleomycin + etoposide + cisplatin or four of etoposide + cisplatin) cures the vast majority of stage II seminomas. Retroperitoneal lymph node dissection (RPLND) is safe in early-stage seminoma, but the risk of relapse is not negligible. Long-term chemotherapy side effects are a reality but may be reduced using de-escalation strategies such as in the SEMITEP trial design, motivated by growing interest in survivorship. RPLND may be an option for well-informed select patients who understand that it may be associated with a higher rate of relapse than with cisplatin-based chemotherapy. In any case, local and systemic treatment should not be performed outside high-volume centers.

Germ cell tumor (GCT) is the most common malignancy among young men (18–40 yr old) and its incidence is rising [1]. Stage II seminoma is defined by the presence of metastases in retroperitoneal lymph nodes (and more rarely the pelvis) without other metastatic deposits. Standard treatment options for stage IIA (lymph nodes <2 cm) and stage IIB (2–5 cm) seminoma classically include either extensive "dog leg" para-aortal/pelvic radiotherapy or chemotherapy with four cycles of etoposide and cisplatin (EP) or three cycles of bleomycin, etoposide, and cisplatin (BEP).

Most experts recommend chemotherapy over radiotherapy for stages IIB and IIC disease (lymph nodes >5 cm) because of high relapse rates after radiation and a higher risk of secondary malignancy [2].

Attempts to reduce the treatment burden for stage II seminoma have been made in recent years, including (1) de-escalation of chemotherapy regimens, (2) combining chemotherapy and radiotherapy, and (3) using retroperitoneal lymph node dissection (RPLND) instead of chemotherapy or radiotherapy.

Two studies recently assessed the safety and efficacy of primary RPLND in stage IIA/B seminoma: the SEMS and PRIMETEST trials [3,4]. These single-arm trials included 55 and 33 patients, respectively. The SEMS trial reported 2-yr relapse-free survival (RFS) of 87% without long-term serious side effects. In the PRIMETEST trial, the 3-yr RFS rate was 69% and 30% of the recurrences were in-field. These data are consistent with patterns of relapse after radiation therapy, reinforcing the idea that local treatment alone may not be sufficient in 20–30% of patients [5,6]. In both cases, mature overall survival (OS) data are still lacking, whereas the cure rate with chemotherapy is approximately 96% [7].

In 2021, the International Germ Cell Cancer Collaborative Group (IGCCCG) published an updated survival estimation for the current era that showed an increase in the 5-yr OS rate [8]. Beyond cure, quality of life in GCT survivors after

DOI of original articles: https://doi.org/10.1016/j.euros.2021.10.005; https://doi.org/10.1016/j.euros.2021.07.009;
* Corresponding author. Department of Cancer Medicine, Institut Gustave Roussy, University of Paris Saclay, 114 Rue Edouard Vaillant, 94805 Villejuif, France.
E-mail address: natacha.naoun@gustaveroussy.fr (N. Naoun).

https://doi.org/10.1016/j.euros.2022.06.010

four EP or three BEP cycles is generally excellent thanks to advances in supportive care [9].

SEMITEP is a nonrandomized, multicenter phase 2 trial assessing whether patients with good IGCCCG–prognosis low-volume metastatic seminoma can be treated with two cycles of EP followed by only one cycle of carboplatin (dose: area under the curve = 7) on the basis of a negative interim fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) [10]. SEMITEP was conducted by the French urogenital tumor study group GETUG and included 102 patients (65% with stage IIA/B GCT): FDG PET/CT findings after two cycles of chemotherapy were negative for 63 patients (67.0%, 95% confidence interval [CI] 57.5–76.5%), who then proceeded to a single cycle of carboplatin. The patients with a positive PET/CT finding proceeded to two additional cycles of EP for a total of four cycles. After median follow-up of 34.4 mo, only eight patients experienced relapse (two in the 4× EP group and six in the carboplatin group). The 2-yr PFS rate was 93.7% in the carboplatin group and 92.9%in the EP group. These data are considered practice-changing by the authors and patients are now routinely treated according to SEMITEP in France.

Another recent phase 2 trial (SAKK 01/10) tested a single dose of carboplatin followed by involved-node radiotherapy as curative treatment for stage IIA/B seminoma [11]. Overall, 120 patients from 20 centers were recruited. The trial achieved 3-yr PFS rates of 95.2% (90% CI 85.5–98.5%) among patients with stage IIA and 92.6% (90% CI 85.2–96.4%) among patients with stage IIB seminoma. A total of seven patients experienced relapse (one clinical stage IIA, six clinical stage IIB), all outside the radiotherapy volumes. Of note, four secondary primary malignancies occurred, all outside the radiation field: two controlateral seminomas treated with orchiectomy, one localized renal clear cell carcinoma, and one cholangiocarcinoma. Full publication and longer-term data are awaited.

Primary chemotherapy remains the main current standard for most patients with stage II seminoma. Given the unique chemosensitivity of this disease and the data from SEMITEP, reducing the chemotherapy burden from four EP or three BEP cycles seems to be now ready for prime time. Given its relapse rate of 20–30%, RPLND should only be regarded as an option, not as a standard, and only for very select patients when performed by experienced surgical teams in this setting following a shared decision-making process with the patient.

The development of biomarkers, notably the promising miRNA-371a-3p [12], is very likely to help in tailoring risk-adapted treatment for GCT, including stage II seminoma.

Conflicts of interest: The authors have nothing to disclose.

References

[1] Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209–49.
[2] Giannatempo P, Greco T, Mariani L, et al. Radiotherapy or chemotherapy for clinical stage IIA and IIB seminoma: a systematic review and meta-analysis of patient outcomes. Ann Oncol 2015;26:657–68.
[3] Daneshmand S, Cary C, Masterson TA, et al. SEMS trial: result of a prospective, multi-institutional phase II clinical trial of surgery in early metastatic seminoma. J Clin Oncol 2021;39(6 Suppl):375.
[4] Albers P, Lusch A, Che Y, Arsov C, Niegisch G, Hiester A. The PRIMETEST trial: prospective phase II trial of primary retroperitoneal lymph node dissection (RPLND) in stage II A/B patients with seminoma. J Clin Oncol 2022;40(6 Suppl):420.
[5] Oldenburg J, Berney DM, Bokemeyer C, et al. Testicular seminoma and non-seminoma: ESMO-EURACAN clinical practice guideline for diagnosis, treatment and follow-up. Ann Oncol 2022;33:362–75.
[6] Chung PWM, Gospodarowicz MK, Panzarella T, et al. Stage II testicular seminoma: patterns of recurrence and outcome of treatment. Eur Urol 2004;45:754–60.
[7] Fizazi K, Delva R, Caty A, et al. A Risk-adapted study of cisplatin and etoposide, with or without ifosfamide, in patients with metastatic seminoma: results of the GETUG S99 multicenter prospective study. Eur Urol 2014;65:381–6.
[8] Gillessen S, Sauvé N, Collette L, et al. Predicting outcomes in men with metastatic nonseminomatous germ cell tumors (NSGCT): results from the IGCCCG Update Consortium. J Clin Oncol 2021;39:1563–74.
[9] Fung C, Sesso HD, Williams AM, et al. Multi-institutional assessment of adverse health outcomes among North American testicular cancer survivors after modern cisplatin-based chemotherapy. J Clin Oncol 2017;35:1211–22.
[10] Loriot Y, Texier M, Culine S, Fléchon A, Thiery-Vuillemin A, Gravis G, et al. The GETUG SEMITEP Trial: De-escalating Chemotherapy in Good-prognosis Seminoma Based on Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography. Eur Urol 2022 Aug;82(2):172–9.
[11] Papachristophilou A, Bedke J, Hayoz S, et al. Single-dose carboplatin followed by involved-node radiotherapy as curative treatment for seminoma stage IIA/B: Efficacy results from the international multicenter phase II trial SAKK 01/10. Ann Oncol 2021;32(Suppl 5):S1283–346. https://doi.org/10.1016/j.annonc.2021.08.2106.
[12] Mego M, Agthoven T, Gronesova P, et al. Clinical utility of plasma miR-371a-3p in germ cell tumors. J Cell Mol Med 2019;23:1128–36.