European Review for Medical and Pharmacological Sciences 2019; 23: 3885-3891

Prognostic and predictive factors in testicular cancer

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Abstract. – OBJECTIVE: Testicular cancer is a relatively rare neoplasia, with an incidence of about 1,5% among male malignancies, usually in the third and fourth decade of life. Although several histological variants are known, with some histotypes affecting older patients (e.g., spermatocytic seminoma), there is a clear predominance (90-95%) of germ cell tumors among young adults patients[1]. Testicular Germ Cell Tumor (TGCT), undoubtedly the seminoma histological variant more than non-seminoma one, is definitely a highly curable disease, with a distinctive sensitivity to cisplatin-based therapy (and for seminomas to radiotherapy) and an outstanding cure rate of nearly 80% even for patients with advanced disease. So far, clinical and pathohistological features supported our efforts to choose the best treatment option for patients suffering from this malignancy, but we don't clearly enough know molecular and pathological features underlying different clinical behaviors, mostly in early-stage disease: by improving this knowledge, we should better "shape" therapeutic or surveillance programs for each patient, also in order to avoid unnecessary, if not harmful, treatments.

Key Words
Testicular cancer, Prognosis, Risk factors, Chemotherapy.

Introduction

Testicular cancer is a relatively rare neoplasia, accounting for the 1.5% of all male malignancies. Some rare variants, such as spermatocytic seminoma, are more frequent in the elderly but the majority of cases, up to 95%, are diagnosed over the third and fourth decade of life, making this tumor, unlike most cancer types, a young adults disease[1].

Testicular Germ Cell Tumor (TGCT), especially seminoma, is a highly curable disease, with a distinctive sensitivity to cisplatin-based chemotherapy and radiation and, even for patients with advanced disease, the cure rate is roughly 80%. Unfortunately the 'non-seminoma' histotype is more aggressive and less sensitive to chemo and radiotherapy, with a significant number of cases associated with poor prognosis. Although clinical and histological elements drive the therapeutic strategy, we still know little about the molecular pathways underlying different clinical behaviour. In early stage, we use clinical elements to choose among adjuvant treatment and surveillance, undoubtedly improving our knowledge of the translational features may help to avoid unnecessary, if not harmful, treatments and to arrange personalized surveillance programs.

Prognostic factors in early stage disease

Seminoma

Stage I includes tumors without node involvement, despite cancer size; however a tumor size greater than 4 cm, together with the infiltration of the 'rete testis', seem to be an independent prognostic factor for hidden metastases[2,3]. Other prognostic factors, such as age at diagnosis and vascular invasion, are under evaluation but their role has not been clarified yet[4,5]. Almost all stage I seminomas

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can be cured, two different strategies can be adopted: (i) adjuvant treatment, either with radiation therapy[6,7] or chemotherapy with single-agent carboplatin[8]; and (ii) a 'wait and watch'-active surveillance[9,10]. For adjuvant treatment, Relapse Rate, RR, is 3-4% and it is equal for patients treated either with radiotherapy or chemotherapy (3-4%); conversely, RR is significantly higher, 15-20%, in patients undergoing active surveillance, probably due to occult nodal metastases at the time of diagnosis. First relapse sites are typically retroperitoneal or high iliac lymph nodes, late recurrence, 10 years or more from the diagnosis, is not rarely observed. As mentioned above, tumor size larger than 4 cm and rete testis infiltration appears to be prognostic markers of occult lymph node involvement, the presence of one or both of these factors lead clinicians to recommend adjuvant treatment rather than surveillance. We can assert that 4/5 of all stage I seminomas are cured with orchiectomy only, while 1/5 is destined to relapse hence may benefit of an adjuvant treatment. How to identify the candidates for postoperative treatment is an open question because we do not have molecular markers. Choosing the 'wait and watch' approach, we expose our patients to a 15-20% more risk of recurrence, giving chemo or radiotherapy the cost in terms of economical and health implications is relevant.

Stage II gathers patients with regional node metastasis: orchiectomy followed by radiotherapy is the main treatment strategy in this group, achieving a 6-years relapse-free survival of 95% for stage IIA (nodal metastases smaller than 2 cm) and 89% for stage IIB (nodal metastases sizing between 2 and 5 cm)[11]. Nevertheless, overall survival is close to 100%[11,12]. Chemotherapy with three cycles of cisplatin, etoposide and bleomycin (PEB), or four cycles of cisplatin and etoposide (PE) is an effective therapeutic option in case of IIB stage disease and IIC (lymph nodes metastases larger than 5 cm)[13]. Carboplatin monotherapy didn't prove to be more effective than radiation therapy in this stage, and it is associated to an increased risk of locoregional or systemic relapse[14].

Non seminoma, NS

Stage I rely on a 99% cure rate, irrespective of the adopted therapeutic strategy, provided it is properly performed[15]. In the case of surveillance, the relapse rate is 27-30%[15,16]. Most common relapse sites are retroperitoneal lymphatic stations, (54-78%) and lungs (13-31%), involvement of more than one visceral organ is very rare[15]. Infiltration of venous or lymphatic vessels is the most impacting prognostic factor in stage I non-seminoma[17,18]. In the study by Read et al[19] the 48% of stage I NS with vascular invasion developed distant metastases compared with the 14-22% in those without it (no adjuvant treatment given in both groups). The proliferation rate, as well as the portion of Embryonal Carcinoma (EC), compared to whole neoplastic tissue, are further prognostic elements, although they did not provide an independent prognostic validity in addition to vascular invasion[20]. NS patients having a EC component (with or without other concomitant histotypes) with a distinct molecular profile (high Ki67, low apoptosis-related proteins expression – determined by a specific test called *TUNEL* – and low p53) seem to have a better survival than patients with opposite features. This classification succeeds to split the good outcome patients from the worst ones in the intermediate/high risk category (identified by the IGCCCG, International Germ Cell Cancer Collaborative Group) but it fails in the good prognosis group. Both, the IGCCCG classification and the molecular one, proved to be, in a multivariate analysis, independent prognostic factors, suggesting their use in clinical practice may improve the clinical decision making process and help to recognize patients candidate to a less intensive treatment regimen[21]. High proliferation index, proven by Ki67 staining, has been associated to higher disease stage or recurrence risk, as already seen in other malignancies, such as breast cancer[22,23], though other works did not find any correlation[24]. To summarize the vascular invasion is the only validated prognostic factor, patients with low recurrence risk (namely those without this pathological feature) should undergo only surveillance, avoiding chemotherapy for 78-86% of patients who shouldn't anyway relapse after surgery[25-27]. If a patient under surveillance relapses, the administration of chemotherapy will result in a cure rate close to 100%.

Yilmaz et al[28] reported that, in addition to vascular invasion, rete testis or hilar soft tissue infiltration is strongly associated to lymph nodes involvement at time of diagnosis, suggesting to routinely assess these features.

In a released retrospective study involving 200 NS patients, EC quote, tumor diameter and treatment strategy (adjuvant therapy *vs.* surveillance only) were found to be, at a logistic regression analysis, recurrence-predicting independent factors, although multivariate analysis confirmed that only adjuvant therapy independently impact Relapse-Free Survival (p-value <0.001; HR 0.54); conversely, vascular invasion did not

significantly affect RFS[29]. In patients not undergoing any adjuvant chemotherapy after orchiectomy, retroperitoneal mass size (<2 cm, IIA, *vs.* 2-5 cm, IIB) and primary tumor vascular invasion are independent prognostic markers for disease recurrence[30]. Nerve sparing retroperitoneal lymph node dissection (NS-RPLND) represents a viable alternative in patients unwilling to undergo surveillance or adjuvant chemotherapy[31,32]; however, it results unnecessary in 50% of cases and with significant surgery-related sequelae[33], such as retrograde ejaculation[34]; furthermore, NS-RPLND does not eliminate the risk of relapse, which remains roughly 10%, with almost all recurrences affecting lung. Adjuvant chemotherapy is not needed if dissected lymph nodes are metastases free (pN0).

In case of high risk of recurrence have adjuvant chemotherapy with two cycles of PEB needs to be considered, undoubtedly, given the absence of molecular prognostic factor, a significant percentage of patients will have chemotherapy without benefiting from it[35-37]; the heavy toxicity associated with such regimen, in particular sexual function impairment, decreased fertility, impact on quality of life, is a hot topic, especially in young patients[38]. Relapses require a more intensive treatment, but complete remission is still achieved in 98% of cases.

Stage II patients with high levels of blood tumor markers, alpha-fetoprotein, AFP, beta chorionic gonadotropin, βHCG, and lactate dehydrogenase, LDH received the same treatment of patients with advanced disease[39].

Patients supposed to be stage IIA without blood markers elevation represent an intriguing issue as CT scan often determines over staging: RPLND allows to directly verify the pathological stage but short-interval follow up, with close monitoring of nodes size and blood markers concentration, may be evaluated. Surgical exploration by RPLND will reveal a pathological stage I (pN0) in 12-13% of patients[40]

Once that stage II has been surgically confirmed adjuvant chemotherapy or surveillance are equally suitable alternatives[41,42]: chemotherapy lowers recurrence rate to less than 7%, but it is really needful only in 30% and 50% of IIA and IIB patients, respectively.

70% of patients with lymph node metastases up to 2 cm, and half of those with nodal lesions sizing between 2 and 5 cm, have to be assumed cured after retroperitoneal lymphatic dissection, whereby adjuvant treatment would result only in chemotherapy side effects and late sequelae.

Residual neoplastic tissue after chemotherapy in stage II patients is not so uncommon; the role of the fluorodeoxyglucose positron emission tomography, FDG-PET, in these cases, especially when blood markers are negative, is under investigation[43,44]. Metabolic assessment shows good sensitivity and specificity in seminomas (92% and 84%, respectively) but appears less useful in NS (77% and 95%, respectively)[45]. In seminoma patients, a post-chemotherapy positive FDG-PET predicts the presence of viable neoplastic tissue[46]. Noteworthy, the best timing of PET assessment is still controversial: an early metabolic complete response, CR, after 2 cycles of PEB seems to suggest that no further treatment is needed[47]; though Bachner et al[48] reported that, by performing scans 6 weeks after chemotherapy, PET sensitivity and specificity, negative predictive value, NPV, and positive predictive value, PPV, were improved to 82%, 90%, 95%, and 69%, respectively, with PET enhanced from 73% before to 88% after this time cut-off.

Prognostic factors in advanced disease

The risk stratification for advanced stage TGCT can be assessed through two models: the first is the union for international cancer control, UICC, TNM staging[49] and the second is the IGCCCG classification[39]; however, the two systems are closely linked to each other and the histology is the main prognostic factor. For the IGCCCG, seminoma patients are divided into good and intermediate risk, depending on presence of *non-pulmonary* visceral metastases (patients with visceral lung metastases are included in the good prognosis group). NS patients have also a poor prognosis group, with 5-years survival roughly 50%, based on serum markers levels and *extra-gonadal* disease (primary mediastinum or primary retroperitoneal tumors).

Unlike the IGCCCG, the TNM staging considers other factors rather than non-pulmonary visceral metastases, such as nodal involvement and serum markers levels, hence patients with liver metastases (or other non-pulmonary visceral sites) are in the same risk group of patients with nodal or pulmonary involvement but with high levels of tumor markers (AFP >10.000 ng/mL, βHCG >50.000 IU/L, LDH >10 times normal): the TNM IIIc group has undoubtedly the worst prognosis at all. The TNM IIIa and IIIb share the same clinical features (pulmonary and/or lyph node lesions), but differ in blood markers concentration: normal in IIIa,

elevated in IIIb (AFP 1.000-10.000 ng/mL, βHCG 5.000-50.000 IU/L, LDH 1.5-10 times normal).

In the TNM system the same criteria, metastatic sites and serum markers concentration, are used for NS: IIIa and IIIb stages include patients with lung and/or nodal disease and mild or intermediate blood markers elevation, respectively; IIIc stage gathers patients with non-pulmonary visceral disease or with lung and/or nodal disease but massive increase in markers levels.

Despite the outstanding cure rate, relapse after cisplatin-based chemotherapy is not a remote event but biological characteristics underlying cisplatin sensitivity are far from being understood: in this regard, p53 alterations and DNA repair cellular device have been suggested to play a key role[50], although a clear evidence has not been demonstrated yet.

p53 and Ki67 expression, assessed by immunohistochemistry, seem to have prognostic significance in the advanced setting, and have been suggested to improve the accuracy of the IGCCCG prognostic system, but further studies are needed to validate such approach[51].

A large, multicenter international trial attempted to point out clinical features which should predict the outcome after failure of first line chemotherapy: histology, primary tumor location, progression-free interval, serum markers level (AFP, βHCG, and LDH), presence of liver, bone, or brain metastases were found to be independent prognostic variables and used to create a prognostic model[52]. At recurrence high dose chemotherapy, HDC, plus autologous stem cell rescue, ASCR, became common use in 1980s, and proved to be an effective strategy in platinum-refractory disease, with long-lasting remissions up to 40%[53]. Nevertheless, a recently published systematic review found no significant difference for standard-dose chemotherapy *vs.* HDCT in survival (in terms of median overall survival, OS, or 1-to-5 year survival rate), those two strategies showed comparable efficacy as salvage therapies in recurrent TGCTs: however, authors highlightened the unmet need of selecting patients more likely to benefit from intensive treatments[54].

Spermatocytic seminoma, deserves special attention, this is a very rare variant of classic seminoma (less than 1% of all TGCTs) and it is characterized by intriguing features: inability to metastasize, unless of a sarcomatous component, and favorable outcome[55]. Such biologic behavior makes this neoplasia even more curable than classic seminoma; comparison studies could be very attractive to elucidate the molecular basis of these differences.

Conclusions

Our knowledge about driving mutations and molecular pathways underlying cancer formation in TGCT is inferior compared to other malignancies such as colorectal or breast cancer, which are indeed more frequent. Nevertheless, new prognostic and predictive factors are under development. The Tissue Micro Arrays, TMA, technology represents a new frontier of translational research in oncology and it has an emerging role in TGCTs as demonstrated in several retrospective series[56]. An over-expression of the transcription factor Brachyury has been associated with more aggressive disease and the immunohistochemistry assessment of such protein has been suggested as innovative test to predict prognosis and as potential oncotarget[57]. Other interesting biomarkers (firstly CpH methylation) have been described by Shen et al[58] focused on a series of 137 TGCTs which were evaluated for genomics and proteomics. Given the high chemotherapy sensitivity the main endpoints should be to find markers of response to limit unnecessary treatments and to improve survival in patients resistant to traditional drugs; in this context a lot of work is going on with immunotherapy though the first data about pembrolizumab are negative[59]. More research effort is needed to understand disease biology and identify tools for patients selection.

Grant Support

This work was supported by grant "Progetto ONCONET 2.0 – Linea progettuale 14 per l'implementazione della prevenzione e diagnosi precoce del tumore alla prostata e testicolo – Regione Campania, Italy" (to G.F.) and by L.I.L.T. (Lega Italiana per la Lotta contro i Tumori) di Napoli.

Conflict of Interests

The Authors declare that they have no conflict of interests.

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