Editorial

Targeted therapies for the treatment of patients with advanced, recurrent or relapsed thymic epithelial tumours

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Thymic epithelial tumours (TETs) are rare neoplasms of the anterior mediastinum with a reported incidence of 0.15 per million person-year in the United States (1). They are classified into thymomas and thymic carcinomas on the basis of morphological features, the grade of atypia of epithelial cells and their relative proportion to lymphocytes.

Thymomas are characterized by an indolent behaviour with a tendency toward local recurrence while thymic carcinomas are more aggressive and frequently present with systemic involvement (2). Surgery is the mainstay of treatment for TETs as well as the only curative option. Unfortunately, about 30% of patients with thymoma and 50–60% with thymic carcinoma are diagnosed with locally advanced or metastatic disease, or recurrent disease after primary therapy not amenable to iterative surgical resection (3).

These patients are currently treated with chemotherapy and radiotherapy. Among first-line chemotherapy regimens, the standard of care is represented by platinum-based regimens such as PAC (doxorubicin, cisplatin, cyclophosphamide) or ADOC (doxorubicin, cisplatin, vincristine, cyclophosphamide) for thymoma (4,5) and carboplatin/paclitaxel for thymic carcinoma patients and thymoma patients who are not fit for anthracycline-based regimens (6).

Durable and high response rates can be obtained with these regimens, varying from 30% to 70% (7); however, the disease invariably recurs and no standard second-line treatments are available after failure of platinum-based chemotherapy. Moreover, anthracyclines have cumulative dose-related cardiac toxicity, which limits their use after the first-line setting.

Several agents have been tried as second-line therapy such as etoposide, ifosfamide, pemetrexed, 5-FU or analogs, gemcitabine, and paclitaxel (8), but unfortunately, these agents have only modest efficacy, and currently, no effective standard treatment is available for refractory metastatic TETs.

Over the past years, the efforts of scientific research have been directed towards the characterization of aberrant molecular pathways involved in the carcinogenesis of thymoma, with the aim of finding potentially targetable molecular abnormalities. In particular, investigators have focused on the mutational status of several genes such as EGFR (9), VEGF (10) and IGF-1R (11,12). Supported by the results of these studies, and by the efficacy previously showed in many other solid tumours, targeted drugs have been tested in those selected patients with advanced TETs and a positive mutational status (13,14). The encouraging results obtained by these anecdotal case reports led to formal investigation of targeted therapies into prospective clinical trials as second-line treatment in patients with advanced recurrent or refractory TETs, regardless of their mutational status.

The article published in December 2017 by Zucali and colleagues on the *Journal of Clinical Oncology* represents one of the most recent studies on this topic. From February 2011 to October 2013, the authors enrolled 51 subjects from seven Italian centres with pathologically confirmed advanced thymoma (n=32) or thymic carcinoma (n=18) who had failed at least one previous line of platinum-based chemotherapy. Patients received oral everolimus 10 mg once daily until disease progression, unacceptable toxicity, death,

or discontinuation for any other reason. After a median treatment duration of 8.4 months, complete remission was observed in one patient (2%), partial response in 5 (10%) and stable disease in 38 (76%), with an overall disease control rate of 88%. Median progression-free survival was 10.1 months, median overall survival was 25.7 months and median time to treatment failure was 8.4 months. The toxicity profile was in line with previous studies, with 28% of patients experiencing grade 3/4 toxicity, which required definitive treatment interruption in 18% of cases. However, a high incidence of pneumonitis was observed (36% of patients), including three cases of fatal pneumonia. The authors concluded that everolimus might induce durable disease control in a high percentage of patients affected by TETs (15).

Although the activity of mTOR inhibitors in TETs was already shown by previous small case series (16), this is the first formal prospective trial designed to test their efficacy. The observed outcomes are intriguing and warrant without doubt further investigations.

Over the past years, several targeted agents have been tested in clinical trials with varying results. Despite the finding of EGFR over-expression in a high percentage of thymomas and thymic carcinomas (17), two clinical phase II trials with EGFR inhibitors yielded disappointing results (18,19). Imatinib, a tyrosine kinase inhibitor, showed activity only in case reports of patients harbouring activating mutations of KIT (20); however, several phase II trials evaluating its efficacy in unselected TETs patients failed to show any survival benefit (21,22). The inhibitor of IGF-1R cixutumumab, tested in a prospective clinical trial enrolling 49 patients with advanced platinum-refractory TET, provided interesting outcomes; in the subset of patients with thymoma, 14% of 37 patients achieved a partial response, 76% stable disease and 11% progressive disease, median time to progression was 8.2 months and median overall survival 16.2 months. In the thymic carcinoma subgroup on the other hand, cixutumumab's activity was unsatisfactory (23). Others encouraging results were obtained in a phase II trial with sunitinib, a multikinase inhibitor with antiangiogenic potential, who demonstrated greater activity in the cohort of patients with thymic carcinoma (24).

A review of all clinical trials of targeted therapies in advanced TETs is beyond the scope of the present paper; however, based on available data, it is possible to affirm that, after early failures, this class of agents now represents a promising therapeutic option in a subset of patients for which there is currently no standard second-line treatment.

Unfortunately, experimental studies concerning patients affected by thymic malignancies share some limitations. In particular, the major obstacle is represented by the rarity of thymoma, which causes low accrual rates in clinical trials. Secondary, due to the relatively indolent behaviour of the disease, there is a significant heterogeneity among studies in reporting results after chemotherapy. Outcome measures based on recurrence, rather than on survival, seem more adequate for this purpose. Third, thymoma and thymic carcinoma are distinct entities characterized by a significant histologic heterogeneity, and data of clinical trials should always be interpreted separately depending on tumor histotype.

The paper by Zucali and colleagues represents a significant contribution to the literature, in that the study population is one of the largest between other similar phase II trials, and the obtained results are remarkable, considering that patients had a chemo-refractory disease and in some cases were heavily pretreated. However, the risk of pneumonitis is non-negligible and should be taken into consideration. It is unclear if tumour type or other clinical characteristics play a role as specific risk factors for this adverse event.

Thanks to these well-conducted clinical trials, it is possible to gain more insight into the role of targeted agents for the treatment of TETs. Further steps forward will be accomplished through a deeper understanding on the molecular signaling pathways implicated in the carcinogenetic process. In the near future, it is possible to predict that genomic analyses will improve the selection of the therapeutic agent based on the molecular signature of the patient (personalized medicine). Moreover, combination chemotherapy with conventional and targeted agents still has to be explored and may offer additional clinical benefits.

Nevertheless, before definitive incorporation in clinical practice several open questions remain to be answered, concerning the efficacy of such agents in unselected patient's cohorts and their specific toxicity profile. Given the rarity of thymic malignancies, only other similar multicentric trials will help us better clarify all these aspects. Thus, it cannot be over-emphasized how important it is that patients affected by TETs be referred to high-volume specialized centers.

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Footnote

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