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EDITORIAL

Chemotherapy should not yet be considered in patients with hormone-sensitive metastatic prostate cancer☆

La quimioterapia no debería todavía ser considerada en los pacientes con cáncer de próstata metastásico hormonosensible

Since 2004, the docetaxel–prednisone combination has been the standard treatment for patients with castration-resistant prostate cancer (CRPC).[1,2] Compared with mitoxantrone–prednisone, it showed an overall survival increase of almost 2 months, significant improvements in pain control in 35% of patients, and a PSA $\geq$ 50% response in 45%. In 32%, grade 3–4 neutropenia was observed and in 3% febrile neutropenia.

In recent years, hormone-based treatments (abiraterone acetate, enzalutamide), targeting progression-related mechanisms involving the androgen receptor (ARTT), have demonstrated at least equivalent efficacy in terms of overall progression-free survival, with excellent tolerance in patients with CRPC.[3–6]

Recently, different studies have evaluated the role of the combination castration-chemotherapy with docetaxel in metastatic patients who had not previously been castrated. Their justification would be based on the possibility of acting precociously on androgen-independent clones, acting more effectively on cells weakened by androgenic suppression (AS) and on greater accessibility of patients to chemotherapy, given the risk that in later stages they might not be in a position to receive it. Against its use, one could argue a possible deleterious effect on immunity in a massive apoptotic induction phase, or the fact that AS takes the cells out of cycle making them less sensitive to chemotherapy.

In the year 2013, GTUG-AFU-15 was published, a European study with recruitment between 2004 and 2008 where 385 patients were randomized, of whom 192 received chemotherapy with docetaxel and prednisone at standard doses associated with AS and 193 received AS alone.[7] Only 10% had visceral metastases. After a mean follow-up of 50 months, the docetaxel group showed a survival advantage of 4 months, which was not statistically significant. In contrast, increased toxicity was observed, mainly neutropenia (32% grades 3–4), with 3% febrile neutropenia and 2% mortality. The quality of life perceived by the patient worsened during treatment with docetaxel, but it was similar in the 2 groups at 12 months. Due to these observations, it was concluded that such combination was inappropriate for this type of patients. It should be noted that during the inclusion period of this trial, the new ARTT were not available, so only 10% received abiraterone and 5% enzalutamide in the context of clinical trial.

In 2014, at the 50th ASCO Congress, the results of the CHAARTED study, published in 2015, were released. It is an American study carried out between 2006 and 2012, where 790 patients were randomized, of which 397 received chemotherapy with docetaxel and prednisone at standard doses associated with AS and 393 received AS alone.[8,9] 66% of the patients had a high volume metastatic disease defined as the presence of visceral metastases (about 15%) or $\geq$4 bone metastases with one or more located outside the spine or pelvis. After a median follow-up of 29 months, there was an increase in survival of the combination group of 13.6 months, limited exclusively to those with a high tumor burden. Likewise, the time of development of resistance to castration (11.7 vs. 20.2 months) was extended by 9 months. Some kind of severe grade 4–5 toxicity was observed in 13% of those treated with chemotherapy, grade 3–4 neutropenia in slightly more than 10% (compared to 30% GETUG) and febrile neutropenia in 2%.

Such promising results required a comparison with GETUG-15. The observed differences could be attributed

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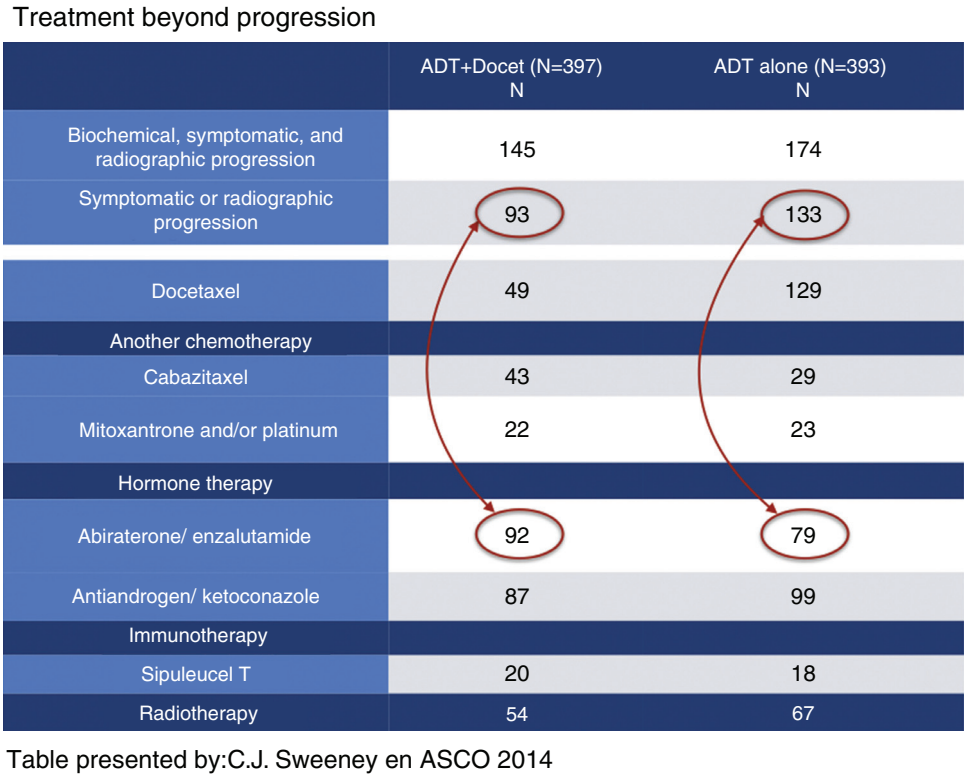

Figure 1 CHAARTED. Treatments to progression. Presented at the ASCO Annual Meeting 2014 by Christopher Sweeney.

to one or the combination of the following causes: that the European study lacked the necessary sample size; that the population (casuistry) was different; or that, since most patients in CHAARTED received treatment for progression with ARTT, with demonstrated efficacy in the increase of survival, the arms were not balanced with regard to these treatments. Indeed, CHAARTED doubles the sample size and the type of patients included is different from GETUG, with a higher presence of visceral involvement and high-burden metastatic disease (52% GETUG vs 66% CHAARTED), which translates into the lower survival observed in the group treated with AS (54 months in GETUG vs 44 months in CHAARTED), so the first 2 hypotheses could justify the observed differences.

However, according to the results presented by the authors, and although in the publication they indicate that the differences were detected already before having these treatments, the patients of the experimental group seem to have received at progression more ARTT than the arm that receives only AS, as it can be seen in the table presented at ASCO (Fig. 1). If, as usual in clinical practice, progression for clinical or radiological reasons is considered as treatment criterion, 92 out of 93 (98%) of the experimental group would have received abiraterone or enzalutamide treatment on progression, compared to only 79 of 133 (59%) in the AS monotherapy arm, a difference of 39%. If we consider all those who progress, including those who do it due to PSA, 92 of 145 (63%) receive treatment with abiraterone or enzalutamide on progression compared to 79 of 174 (45%), resulting in a difference of 18%. If these data presented in ASCO are true, the observed benefit could also be attributed to the new ARTTs and not to chemotherapy, which would nullify its conclusions.

In the study publication, surprisingly, the survival data correspond to December 2013 (those presented in ASCO), whereas the table with data of the treatments received on progression, published in a separated appendix, are from December 2014, that is, a year later (Fig. 2), so the difference could have been masked.[9] No less surprising, if we compare both tables, is the fact that, having almost doubled the number of patients with clinical–radiological progression (from 93 to 180) between 2013 and 2014, only 13 patients out of the 87 (15%) who progressed in 2014 have received treatments with abiraterone or enzalutamide, something completely outside the usual clinical practice (Fig. 3). Therefore, it is urgent to clarify these discordances so that this study is taken into account, given the severe implications that derive from it.

This is of particular importance if we take into account the observation in GETUG-15 of a decrease in the beneficial effect of long-term chemotherapy that the authors consider a possible justification for the absence of observed benefit in overall survival, despite the good initial clinical–biological responses (PSA).[7] In addition, subsequent sub-analyses performed on the GETUG study, applying the CHAARTED tumor burden, do not show any survival benefit, nor in the high-burden group.[10]

In December 2015, the STAMPEDE study, a multi-arm and stage design study was published, one of which includes the addition of docetaxel to AS in patients with high-risk and metastatic tumors with the same objectives as the previous ones.[11] Focusing on the last subgroup, between 2005 and