Correspondence

Timing of androgen-deprivation therapy for prostate cancer: still a long way to go

We read with interest the article in The Lancet Oncology by Gillian Duchesne and colleagues1 on their study assessing the optimum timing (immediate vs delayed) of androgen-deprivation therapy for men with prostate cancer who have a rising concentration of prostate-specific antigen (PSA) even after curative therapy, or who are considered not suitable for curative treatment. This topic has a major impact on clinical practice, especially for patients affected by biochemical recurrence after local treatment, considering that approximately 30% of men experience a rise in PSA after both radical prostatectomy2 and radiation therapy.3 Although optimum timing of androgen-deprivation therapy has been assessed in previous clinical trials,4 the novelty of Duchesne and colleagues’ study lies in the assessment of asymptomatic patients only. However, the following points deserve discussion.

First, the group of patients eligible for the trial on the basis of PSA recurrence after curative treatment (radical prostatectomy alone, radiotherapy alone, or radical prostatectomy followed by salvage radiotherapy) included patients with extremely different disease stages, levels of disease progression, and prognoses. Moreover, asymptomatic patients unsuitable for curative treatment because of age and comorbidities were also included. Hence, the clinical heterogeneity within, and across groups, was extremely high, and the hypothesis of the study sounds unspecific and too vague for a randomised clinical trial.

Second, the investigators stratified patients by type of previous treatment, relapse-free interval, PSA doubling time, androgen-deprivation therapy schedule, and metastases stage; however, tumour characteristics (such as tumour stage and Gleason score) were not taken into account although they represent well known prognostic factors for outcomes after radical prostatectomy,4 radiotherapy,5 and salvage radiotherapy.5

Third, Duchesne and colleagues concluded that immediate receipt of androgen-deprivation therapy significantly improved overall survival compared with delayed intervention. However, in the overall population the unadjusted hazard ratio (HR) for overall survival for immediate intervention versus delayed intervention was 0·55 (95% CI 0·30–1·00; p=0·050), which was not significant after adjusted Cox regression analysis (0·54, 0·27–1·06; p=0·074). Additionally, when considering the PSA-relapse subgroup population only, no significant differences were noted between treatment groups for either the unadjusted HR (0·58, 95% CI 0·30–1·12; p=0·10) or the adjusted HR (0·59, 0·26–1·30; p=0·19). Furthermore, the survival difference became evident after at least 5 years, as patients unsuitable for curative treatment had a lower life expectancy because of age and comorbidities. Taken together, these findings are far from proving a clear survival benefit of immediate versus delayed androgen-deprivation therapy.

In conclusion, the results of Duchesne and colleagues’ study should be interpreted with caution and contextualised on the basis of different clinical scenarios. Initial hypothesis, patient population, and randomisation type all play an essential role in the outcome of androgen-deprivation therapy, despite the high level of evidence from this randomised clinical trial.

We declare no competing interests.

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Authors’ reply

We agree with Nicola Fossati and colleagues that the results of our trial1 on the timing of androgen-deprivation therapy are not the final answer and need to be interpreted with some caution, accounting for the clinical characteristics of individual patients. Nonetheless, the trial has provided some useful evidence in a scenario where previously there was no evidence at all.

We do not agree with their interpretation of the three key limitations of the evidence. With respect to our trial design and patient stratification, a distinction needs to be made between prognostic factors at the time of diagnosis and those at the time of relapse, when patients have shown themselves to be high risk by not remaining in remission. Patients with particularly poor characteristics at