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Review

Medical treatment for biochemical relapse after radiotherapy

Traitements médicaux de la rechute biochimique après radiothérapie

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ABSTRACT

This article's purpose was to review the medical data justifying the use of a medical treatment for biochemical relapse after external beam radiotherapy. The MEDLINE database was searched to identify relevant information with the following medical subject headings: "prostate cancer", "radiotherapy" and "biochemical relapse". Prognostic factors affecting the overall survival of patients with a biochemical relapse after external beam radiotherapy have been identified: short prostate specific antigen (PSA)-doubling time (< 12 months), high PSA value (> 10 ng/mL) and short interval between treatment and biochemical relapse (< 18 months). If a second local treatment is not feasible, timing to initiate a salvage medical treatment is not defined. Particularly, randomized trials did not demonstrate a significant benefit of an early initiation of androgen deprivation treatment. Some retrospective studies suggest that an early androgen deprivation is justified if poor prognostic factors are found. However, if an androgen deprivation treatment is prescribed, intermittent schedule is non-inferior to a continuous administration and seems to offer a better quality of life. Many non-hormonal treatments have also been evaluated in this setting: only 5-alpha-reductase inhibitors could be proposed in some specific situations. In conclusion, the judicious use of a medical treatment for biochemical relapse is still debated. Given the natural history of this clinical situation, a simple surveillance is justified in many cases.

Mots clés :
Rechute biochimique
Cancer de la prostate
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RÉSUMÉ

L'objectif de cette mise au point était d'analyser les données de la littérature concernant les traitements médicaux de la rechute biochimique après radiothérapie du cancer de la prostate. La base de données MEDLINE a été interrogée avec les mots clés suivants : *prostate cancer*, *radiotherapy* et *biochemical relapse*. Les facteurs pronostiques affectant la survie globale des patients avec une rechute biochimique après radiothérapie sont bien identifiés : temps de doublement de la concentration d'antigène spécifique de la prostate (PSA) court (moins de 12 mois), concentration de PSA élevée (plus de 10 ng/mL) et court intervalle entre la fin du traitement initial et la rechute (moins de 18 mois). Si un second traitement local n'est pas envisageable, le moment optimal pour débuter un traitement médical de rattrapage n'est pas défini. Les essais randomisés existants n'ont, en particulier, pas démontré de bénéfice significatif en faveur d'une administration précoce d'une hormonothérapie dans ce contexte. Quelques études rétrospectives suggèrent qu'une privation androgénique précoce serait justifiée s'il existe des facteurs de pronostic défavorable. Si une hormonothérapie doit être prescrite, le traitement intermittent est statistiquement équivalent au traitement continu et semble être mieux toléré. De nombreux traitements non hormonaux ont également été évalués dans ce contexte : seuls les inhibiteurs de la 5-alpha-réductase peuvent être proposés dans des circonstances particulières. En conclusion, l'utilisation judicieuse du traitement médical pour des rechutes biochimiques reste débattue. Compte tenu de l'histoire naturelle de cette situation clinique, une simple surveillance est justifiée dans la plupart des cas.

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1. Introduction

After external beam radiotherapy (EBRT), the prostate specific antigen (PSA) level declines progressively to reach its lowest value called nadir. In some cases, a PSA concentration increase is observed. PSA remains the most sensible and specific marker of tumour progression. Currently, no imaging technique is able to improve the sensitivity of PSA. Consequently, in usual practice, only PSA measurement is recommended for surveillance after EBRT. Since 2005, a PSA concentration of 2 ng/mL above the nadir level is defined as a biochemical relapse (Phoenix definition): this definition, internationally adopted, is well correlated to clinical failure [1–3].

2. Natural history of biochemical relapse after EBRT

Spontaneous evolution after biochemical relapse differs from one patient to another: some patients will not have any clinical symptoms during their remaining lifetime, and others will have a clinical evolution a short time after biochemical relapse, will suffer from distant metastasis and will die of their disease.

After surgery, biochemical relapse is defined as a PSA level higher than 0.2 ng/mL. Natural history of biochemical relapse after surgery is now well known [4,5]. The occurrence of metastases is not a frequent event; median time between the biochemical relapse and occurrence of distant metastases is 8 years and between metastases and death 5 years [6]. Specific survival rates at 5, 10 and 15 years after biochemical relapse are 93%, 73% and 55% [6]. The most important prognostic factors are PSA doubling time, Gleason score on the surgical specimen and interval between surgery and the time of biochemical relapse. Many authors also reported the importance of PSA kinetics as a prognostic factor [7,8].

After EBRT, biochemical relapse is associated with an increase in mortality, but this effect is only seen after 10 years [9]. In a series of 381 patients with a biochemical relapse, only 29% had distant metastases in the first 5 years; overall survival was 79%, half of the deaths were related to non-cancer diseases [10].

The most important prognostic factor for specific survival is the PSA doubling time [10–14]. Calculation of the PSA doubling time requires at least three dosages. The easiest way to obtain its value is on the website of the Memorial Sloan Kettering [49]. The PSA doubling time is correlated to the occurrence of distant metastasis, cause-specific survival and in some series to overall survival [15]. Among 234 patients with a biochemical relapse after EBRT, metastatic evolution occurred in 45.9% of patients of the PSA doubling time is lower than 6 months, against 7.7% if the PSA doubling time is higher than 6 months [14]. For patients with a PSA doubling time less than 3 months, median survival from the biochemical relapse is 6 years versus 10 years if the PSA doubling time is longer than 12 months [11].

Another important prognostic factor is the interval between the end of the initial treatment and the biochemical relapse: it has been shown that an interval less than 18 months is associated with a higher risk of distant metastasis and prostate cancer deaths [16].

3. What staging technique should be used to detect biochemical relapse?

Biochemical relapse is defined as the asymptomatic increase of PSA with no evidence of disease on imaging studies. Previously, only bone scan and CT scan were performed in case of biochemical relapse after EBRT, with a low sensitivity to define the anatomical site of the relapse. Given the opportunity to propose to some patients a second local treatment, PET/CT with ^{11}C or ^{18}F tracers is now more often performed in case of biochemical relapse [48]. This imaging technique can detect nodal or metastatic sites earlier than previous techniques. In a recent series, (^{11}C)-choline PET/CT was able to detect the site of relapse in 123/140 patients (87.8%) with a biochemical relapse (nadir + 2 ng/mL) after EBRT [17]. It could be proposed as soon as the PSA level is higher than 2 ng/mL.

Its main indication is to define the population of patients eligible for a second local treatment. However, it can also discriminate patients with a low tumour burden from those with an already disseminated disease. It has been shown that (^{11}C)-choline PET/CT has a prognostic value for biochemical relapse after surgery: patients with negative PET/CT or locoregional recurrence had a better survival rate than those with a disseminated disease [18]. This could have some implications when the decision of a medical treatment is debated.

4. When to start a medical treatment after biochemical relapse?

Because the natural history after biochemical relapse is often indolent, its treatment may be delayed. Once again, biochemical relapse must be considered as a surrogate marker for long-term survival and as an end-point definition for clinical trials. This is a methodological tool. Its usefulness in routine practice is doubtful.

If a second local treatment, with a curative intent, is considered, it probably must be performed as soon as possible. But the curative potential of a medical treatment, and particularly androgen deprivation, has not been demonstrated. Moreover, this population is often old; a potential benefit in survival is often masked by non-cancer related deaths.

Androgen deprivation is the most widely used treatment after biochemical relapse. In fact, in a survey published in 2008, 93.5% of the patients experiencing a biochemical relapse after EBRT underwent androgen deprivation [19]. It seems that the response rate of a salvage androgen deprivation is not influenced by a previous hormonal treatment given with EBRT [20]. Androgen deprivation can cause significant quality of life-lowering toxicity, including hot flushes, fatigue, anemia and metabolic syndrome. Moreover, it has been established that androgen deprivation could induce cardiovascular and bone events [21]. This treatment must not be given to all patients with a biochemical relapse but only to those in which a benefit in survival or in survival without cancer symptoms can be obtained.

The benefit of an early compared to a delayed androgen deprivation has been extensively discussed in the literature. No specific trial exploring biochemical relapse has been conducted. Three large randomised trials have been designed in patients with a locally advanced or asymptomatic metastatic prostate cancer, comparing early to delayed androgen deprivation in cases of cancer symptoms. It seems interesting to review these trials before analysing the experiences for biochemical relapse.

4.1. Prospective trials of delayed androgen deprivation in locally advanced or metastatic disease

In the United Kingdom, the Medical Research Council (MRC) conducted a prospective trial in 908 patients with an asymptomatic metastatic prostate cancer or a locally advanced disease, not candidate for a local treatment [22]. Early androgen deprivation improved the outcome in non-metastatic patients but not in the others. On the other hand, in the metastatic group, a decrease in cancer complications (urinary obstruction spinal cord compression, pathological fractures, etc.) was observed.

The results of a Swiss trial, where only 20% among 197 patients were metastatic, showed that early androgen deprivation did not delay the occurrence of cancer symptoms and did not improve