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Review article

Gemcitabine-based chemotherapy in sarcomas: A systematic review of published trials

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ABSTRACT

Gemcitabine is largely used in the management of sarcomas. We have systematically reviewed all of the fully published trials that investigated a gemcitabine-based regimen in the management of sarcomas and then provided a grade of recommendations and a level of evidence for every recommendation. Because of conflicting results from successive non-randomized phase II trials, gemcitabine activity alone in unselected pretreated soft tissue sarcomas could not be properly assessed. Gemcitabine alone and gemcitabine-docetaxel appeared to both be active in pretreated uterine and non-uterine leiomyosarcoma (1B;I). Gemcitabine–dacarbazine appeared to be active in pretreated unselected soft tissue sarcomas (1B;I). According the GeDDIS phase III trial (not yet fully published), gemcitabine-docetaxel appeared slightly less active than doxorubicine and more toxic than doxorubicine in chemo-naïve metastatic soft tissue sarcoma patients. Because of the absence of controlled randomized trials, the benefit of gemcitabine-docetaxel as an adjuvant treatment in high-grade uterine leiomyosarcoma could

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not be appropriately assessed. The level of activity of gemcitabine/docetaxel in bone sarcomas cannot be ascertained with the available data. The level of evidence supporting the use of gemcitabine-based regimens in sarcoma management is limited. Confirmatory phase III trials are warranted when phase II trials suggest some preliminary activity.

1. Introduction

Sarcomas represent approximately 2% of all adult cancers (Siegel et al., 2012; Mastrangelo et al., 2012). They constitute a heterogeneous group of tumors in terms of histology (Mastrangelo et al., 2012; Coindre et al., 2001), clinical behavior (Coindre et al., 2001), location and sensitivity to systemic treatments (Penel et al., 2011; ESMO et al., 2012). Currently, doxorubicin-based chemotherapy, in particular, doxorubicin as a single-agent, remains the best choice as a first-line treatment in adult soft tissue sarcoma that is not amenable to curative-intent surgery (ESMO et al., 2012). Beyond this first-line of treatment, there is no consensual salvage therapy; nevertheless, some drugs and combinations (ifosfamide, dacarbazine, trabectedin, pazopanib, etc.) in phase II trials have demonstrated signs of anti-tumor activity (Penel et al., 2011; ESMO et al., 2012). Four years ago, we noted the inconsistent results of trials investigating the activity of gemcitabine alone or gemcitabine-docetaxel in combination as salvage treatments in adults with soft tissue sarcomas (Penel et al., 2011). Nevertheless, in 2012, the EORTC Soft-Tissue and Bone Sarcoma Group (EORTC-STBSG) stressed that approximately 39% of Nord-American and European patients with advanced soft tissue sarcomas received gemcitabine before study entry in the Palette trial comparing pazopanib versus a placebo; nineteen percent of patients received gemcitabine after this study (Marreaud et al., 2012). Despite conflicting results from successive phase II trials, gemcitabine is widely used in the treatment of sarcoma patients.

Regarding these facts, here, we propose a systematic review of published clinical trials investigating the activity of gemcitabine-based chemotherapy in advanced sarcomas.

2. Materials and methods

2.1. Data extraction

Using Medline, we reviewed all of the phase II clinical trials fulfilling the following criteria: (i) trials specifically focusing on sarcoma patients, (ii) trials published in the English literature and (iii) trials published between January 1997 and March 2015. For all of the published trials, we extracted the following data: nature of the regimen, number of treated patients, best overall objective response rate, best tumor control rate (including stable disease and objective response according to the used system RECIST or WHO), median progression-free, 3 and 6-month progression-free rates (3-month and 6-month PFR) and overall survival rates.

2.2. Definition of active drug

To estimate the anti-tumor activity of gemcitabine-based protocols in soft tissue sarcoma patients, we used the EORTC-STBSG criteria as a reference (Van Glabbeke et al., 2002). For first-line therapy, a 6-month PFR of ≥30–56% (depending on histology; 40% in the case of leiomyosarcoma) can be regarded as a sign of drug activity; for second- or latter line therapy, a 3-month PFR of ≥40% suggested drug activity and <20% suggested inactivity (Van Glabbeke et al., 2002).

Such definitions and thresholds do not exist in bone sarcoma cases.

2.3. Recommendations

We then applied the level of evidence and grade of recommendations as defined by the U.S. Preventive Services Task Force (Harris et al., 2001) and by the American College of Chest Physicians task force (West et al., 2002) (see online appendixes 1 and 2).

3. Results

3.1. Gemcitabine-based chemotherapy as second- or latter line treatments in soft tissue sarcomas

Three gemcitabine-based regimens were assessed in patients with soft tissue sarcoma that was previously treated with at least one line of anthracyclin-containing chemotherapy: gemcitabine alone (Spaeth-Schwalbe et al., 2000; Patel et al., 2001; Svancarova et al., 2002; Hartmann et al., 2006; Ferraresi et al., 2008; Pautier et al., 2012), gemcitabine plus docetaxel (Ferraresi et al., 2008; Pautier et al., 2012; Hensley et al., 2002, 2008a) or gemcitabine plus dacabazine (Takano et al., 2014). Two clinical trials were randomized phase II trials: gemcitabine versus gemcitabine plus docetaxel (Ferraresi et al., 2008) and gemcitabine plus dacarbazine versus dacarbazine (Hensley et al., 2008a).

3.1.1. Gemcitabine alone as salvage therapy

Six single-arm phase II studies assessed the activity of gemcitabine alone in anthracyclin-refractory soft tissue sarcoma patients (Spaeth-Schwalbe et al., 2000; Patel et al., 2001; Svancarova et al., 2002; Hartmann et al., 2006; Ferraresi et al., 2008; Pautier et al., 2012) (Table 1). Different schedules were administered, rendering the overview as very confusing. Gemcitabine was administered over 30 min in 3 studies (Patel et al., 2001; Svancarova et al., 2002; Hartmann et al., 2006), over 100 min in 2 studies (Ferraresi et al., 2008; Pautier et al., 2012) and over 360 min in 1 study (Spaeth-Schwalbe et al., 2000). The planned dose-intensity of gemcitabine widely varied across the studies, from 200 mg/m^2/week (Spaeth-Schwalbe et al., 2000) to 830 mg/m^2/week (Svancarova et al., 2002). The results can be analyzed in 2 parts: the 5 studies enrolling all histologies (Spaeth-Schwalbe et al., 2000; Patel et al., 2001; Svancarova et al., 2002; Hartmann et al., 2006; Ferraresi et al., 2008) and the study assessing gemcitabine in leiomyosarcoma patients (Pautier et al., 2012).

In unselected patients, the shortest and longest reported median overall survivals were 7.2 (Svancarova et al., 2002) and 13.9 months (Patel et al., 2001), respectively. The reported best objective response rates varied from 3.1% (Svancarova et al., 2002) to 17.9% in non-GIST sarcomas (Patel et al., 2001). The 3-month PFR was available in only 3 studies (Spaeth-Schwalbe et al., 2000; Hartmann et al., 2006; Ferraresi et al., 2008); the pooled 3-month PFR was 19/47 (40.0%). This figure suggests that gemcitabine could be an active drug in an unselected sarcoma but does not take into account the results of 2 large trials (Patel et al., 2001; Svancarova et al., 2002).