RESEARCH ARTICLE

Irinotecan as a Palliative Therapy for Metastatic Breast Cancer Patients after Previous Chemotherapy

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Abstract

Background: This analysis was conducted to evaluate the efficacy and safety of irinotecan based chemotherapy for treatment of patients with metastatic breast cancer (MBC) who experienced disease progression after one to three chemotherapy regimens, including at least one anthracycline- or taxane-based. Methods: Clinical studies were identified using a predefined search strategy. Pooled response rates (RR) to treatment were calculated. Results: As irinotecan based regimens, 5 clinical studies which including 217 patients with refractory MBC were considered eligible for inclusion, with irinotecan, cisplatin, capecitabine, or TS-1. Systemic analysis suggested that, in all patients, pooled RR was 48.8% (106/217) with irinotecan based regimens. Thrombocytopenia and leukocytopenia were the main side effects. No grade III or IV renal or liver toxicity was observed. No treatment related deaths occurred. Conclusion: This systemic analysis suggests that irinotecan based regimens are beneficial and safe for treating patients with MBC after other chemotherapy.

Keywords: Metastatic breast cancer - previous chemotherapy - irinotecan - palliative therapy

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Introduction

It was estimated that 121, 269 new cases of breast cancer were diagnosed in China in 2000 and 168, 013 in 2005 (Yang et al., 2005). The incidence and mortality rate of breast cancer increased significantly in China over the last several decades (Yu et al., 2007). Despite advances in prevention, risk factor reduction, early diagnosis and treatment, breast cancer remains a main public health concern, with more than a million new cases diagnosed annually, resulting in >400, 000 deaths worldwide (Ferlay et al., 2002; Huang et al., 2004).Anthracyclines and taxanes are the two most active classes of cytotoxic agents for early and advanced stage breast cancer, and are thus commonly used as a component of either adjuvant or neoadjuvant therapy (Sparano et al., 2008), and/or in patients with metastatic breast cancer (MBC) (Carrick et al., 2009). Anthracyclines are generally not used for metastatic disease if previously used for adjuvant therapy because of the potential for cumulative cardiac toxicity (Sparano et al., 2009). Anthracyclines are also often not considered even if there has been no prior adjuvant exposure because they are generally less effective than taxanes as first line therapy (Chan et al., 1999; Sledge et al., 2003), and because there are often other alternatives for second-line therapy or beyond.

There are currently three cytotoxic drugs approved for anthracycline and taxane-pretreated MBC, including capecitabine, ixabepilone and eribulin. Some are approved as monotherapy only (eribulin), whereas others are approved either as monotherapy or in combination (capecitabine, ixabepilone). Other agents that are not specifically approved for this indication but are commonly used in clinical practice either alone or in combination with other cytotoxic agents and/or biologics include antimetabolites (gemcitabine), platinum analogues (cisplatin, carboplatin), antitubulins (vinorelbine, docetaxel), topoisomerase I inhibitors (irinotecan), liposomal anthracyclines (pegylated liposomal anthracyclines), and other agents that are rarely used because of their toxicity profile (mitomycin-C).

Irinotecan and its active metabolite, SN-38, interacts with cellular topoisomerase I-DNA complexes and has S-phase-specific cytotoxicity by preventing religation of the DNA strand, resulting in double-strand DNA breakage and cell death (Liu et al., 2000). A randomized phase II study in 103 patients with MBC who had progressive disease after one to three lines of chemotherapy compared irinotecan given IV in a 3 weekly (240 mg/m^2 IV every 3 weeks) or weekly schedule (100 mg/m^2 IV for 4 of 6 weeks). The weekly regimen was associated with more favorable response rate (23% vs 14%) and median PFS (2.8 vs 1.9 months) (Perez et al., 2004). A polymer-containing formulation of SN-38 (etirinotecan pegol) which produces sustained SN-38 blood levels has demonstrated activity in MBC (Gale et al., 2010). A phase

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III trial has been initiated comparing etirinotecan pegol (145 mg/m^2 IV every 3 weeks) with physician's choice of therapy in patients with MBC who have been previously treated with an anthracycline, taxane, and capecitabine (ClinicalTrials. Gov identifier NCT0149210).

According to this background, we hypothesize that irinotecan originated regimen could be established as an optimal schedule for patients with MBC.

Materials and Methods

Search strategy

We searched PUBMED, by using the following search term: (Metastatic breast cancer) and (irinotecan). All clinical studies evaluating the impact of irinotecan on the response or survival and side effects for metastatic breast cancer published in English prior to August 2014 were identified. If samples of two studies overlap, only the newest one was included. Additional articles were obtained from references within the articles identified by the electronic search. We did not consider meeting abstracts or unpublished reports.

Inclusion and exclusion criteria

We reviewed abstracts of all citations and retrieved studies. The following criteria were used to include published studies: (1) Clinical studies, conbined with cisplatin, oxaliplatin or gemcitabine; (2) The study was performed in accordance with the Helsinki Declaration (1964, amended in 1975 and 1983) of the World Medical Association. Eligibility criteria included histologically or cytologically verified metastatic breast cancer, the presence of at least one bidimensionally measurable lesion, a performance status (WHO) ≤2, age ≥18 years. Studies were excluded if one of the following existed: (a) Duplicate data; (b) No sufficient data were reported.

Data collection and analysis

Selection of trials and data extraction: The titles and abstracts of publications identified according to the above search strategy were assessed independently for inclusion by two authors, the full text was selected for further assessment if the abstract suggests relevance. Disagreement was resolved by discussion. Data was extracted by independent authors. The following recorded data were extracted: Author, publication data, country of the first or corresponding author, the number of patients. Outcome measures presented in at least 3 studies were extracted for combined analysis.

Results

There were 52 papers relevant to the search words by the end of February 2014. Via steps of screening the title and reading the abstract, 5 studies were identified (Frasci et al., 2005; Stathopoulos et al., 2005; Moulder et al., 2008; Lee et al., 2013; Otsuka, et al., 2013). These studies had been carried out in China, Japan, Korea, Europe and the USA. The following outcomes were presented in at least all studies and extracted for combined analysis: Response rate, including the rate of complete or partial response (CR or PR) and toxicities. Characteristics of studies included in the meta-analysis are presented as short-term outcomes: The response rate of Otsuka, et al. was 47.1% (16/34), of Lee et al. was 58.3% (21/36), of Moulder SY et al. was 24.5% (12/49), of Frasci et al. was 64% (32/50), and of Stathopoulos et al. was 52.1% (25/48).Totally, 217 patients were enrolled and 106 patients achieved CR or PR, the pooled response rate thus was 106/217 (48.8%). Observation on toxicities: Major adverse effects were hematological toxicities, gastrointestinal disturbance, and neurosensory toxicity.

Discussion

Breast cancer remains a significant problem for women as it is one of the most common cause of tumor-related death world-wide as well as in China (Deng et al., 2013; Engin et al., 2013; Fouz et al., 2013; Liu et al., 2013; Sedighi et al., 2013; Zhu et al., 2013; Wang et al., 2014). When irinotecan is used for treating patients with MBC, several studies should be mentioned. One is a Japanese study comprised 40 patients aged 35-79 years (Otsuka et al., 2013). In this study, Irinotecan was administered at 60 mg/m^2, and was infused on days 1, 8, and 15 for every 4 weeks, and accompanied by TS-1 (at 80 mg/m^2/day orally on days 3-7, 10-14, and 17-21 every 4 weeks) (Otsuka et al., 2013). As results of this study, among 34 patients whose tumor response data were available, the response rate was 47% (1 complete and 15 partial responses); stable disease was observed in 17 patients (50%); one patient had disease progression (3%); median progression-free survival was 14 months; median overall survival was 26 months, and 79.3% of patients survived for 1 year; the most common grade 3 or 4 adverse events were neutropenia, leukopenia, diarrhea, and anemia (Otsuka et al., 2013). However, the response rate is lower in a study conducted in the USA (Moulder et al., 2008). In this American study, patients who had received previous anthracycline therapy or were not candidates for anthracycline therapy received gemcitabine at a dose of 1000 mg/m^2 intravenously over 30 minutes followed by irinotecan at a dose of 100 mg/m^2 over 90 minutes on days 1 and 8 of a 21-day cycle (Moulder et al., 2008). Forty-nine patients were assessed for response. The response rate was approximately 25% (all partial responses, 12 patients). Six patients had stable disease (SD) for > or =6 months for a clinical benefit rate (PR + SD) of 39%. The median time to disease progression was 3.7 months, and median survival was 11.6 months. Toxicities included neutropenia, nausea, and vomiting (Moulder et al., 2008). A high response of irinotecan based regimen in treating breast cancer patients with previous chemotherapy comes from Republic of Korea (Lee et al., 2013). In this study, 36 patients were enrolled to evaluate the efficacy and tolerability of combined treatment with irinotecan and capecitabine. All patients with MBC were anthracycline-and taxane-pretreated. Patients received 80 mg/m^2 irinotecan on days 1 and 8 and 1, 000 mg/m^2 capecitabine twice daily on days 1-14 of 21-day cycles until disease progression. The median follow-up was 47.6 months. The ORR was 58.3%, with 3 complete responses and 18 partial responses. The median PFS

was 7.6 months, and the median OS was 20.0 months. Neutropenia was the most common adverse event with febrile neutropenia in 2 patients. Three patients had grade 3 diarrhea, 3 patients had grade 3 asthenia, and 1 patient had grade 3 hand-foot syndrome (Lee et al., 2013). Further higher responses of irinotecan in treating breast cancer patients with previous chemotherapy were obtained from Italy and Greece (Frasci et al., 2005; Stathopoulos et al., 2005). In study first authored by Frasci, 50 patients (48 with metastatic and 2 with locally advanced disease) were enrolled to evaluate the feasibility and activity of combination treatment with docetaxel and irinotecan, combined with filgrastim support, in anthracycline-and paclitaxel-pretreated MBC patients. Docetaxel (80 mg/m^2) and irinotecan (100 mg/m^2) were given biweekly with filgrastim support (300 microg/day on days 4-7). Thirty-one patients had visceral localizations. All patients in this study had received epirubicin plus paclitaxel, with or without cisplatin, as front-line treatment for advanced disease. In general, fatigue and diarrhea were the main chemotherapy-related toxicities in this study, being severe in 10 (20%) and 4 (8%) patients. Grade 3 or 4 neutropenia and thrombocytopenia occurred in 18 (36%) and 6 (12%) patients, respectively. A total of 32 objective responses were recorded (ORR = 64%), including 8 complete responses (16%). An additional 8 patients showed stable disease. In the study from Greece (Stathopoulos et al., 2005), 48 patients pre-treated with anthracycline-combined chemotherapy, 30 patients were also treated with paclitaxel and 2 with docetaxel, were enrolled. All patients had WHO performance status of 0-2. The main metastasis was in the liver (54.2%), in the lungs (27.1%), in soft tissues (12.5%) and in the skeleton (6.3%).Irinotecan was infused at 200 mg/m^2 for 90 min and docetaxel at 80 mg/m^2 for 90 min, repeated every 3 weeks. As a result, 25 patients had objective responses: 3 complete and 22 partial; the most responsive metastases were observed when liver was the metastatic site (53.9%). Grade 3 and 4 neutropenia was observed in 18 patients (37.5%); 14 (29.2%) patients developed anemia and three (6.3%) thrombocytopenia. Regarding non-haematologic toxicities, alopecia and fatigue were common; grade 3 diarrhea was observed in only one (2.1%) patient (Stathopoulos et al., 2005). However, an American study is associated with low response rate (Perez et al., 2004). In this study, MBC patients who experienced disease progression after one to three chemotherapeutic regimens, including at least one anthracycline-or taxane-based regimen, were randomly assigned to irinotecan in 6-week cycles comprising 100 mg/m^2 weekly for 4 weeks, then a 2-week rest (weekly) or 240 mg/m^2 every 3 weeks (Perez et al., 2004). As the result suggested that the weekly arm had 52 assessable patients; the every-3-weeks arm had 51 assessable patients. In the weekly arm, the objective response rate was 23% (one CR, 11 PR). Median overall survival was 9.7 months. In the every-3-weeks arm, the objective response rate was 14% (nine PR), and median overall survival was 8.6 months. Treatment was well tolerated, especially in the weekly arm. Grade 3 to 4 adverse events with > or = 10% incidence included neutropenia (29%) and diarrhea (17%) in the weekly arm and neutropenia (36%), vomiting (20%), dyspnea (18%), nausea (16%), and diarrhea (12%) in the every-3-weeks arm (Perez et al., 2004).

Our current systemic analysis revealed that in irinotecan based 5 clinical studies which including 217 patients with refractory MBC, pooled RR was 48.8% (106/217). Thrombocytopenia and leukocytopenia were the main side effects. No grade III or IV renal or liver toxicity were observed. No treatment related death occurred in irinotecan based treatment. In conclusion: Our systemic analysis suggests that irinotecan based regimens is active and safe in treating pagtients with MBC.

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