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Systematic review

Concurrent administration of anti-HER2 therapy and radiotherapy: Systematic review

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ABSTRACT

Background: Over the past few years, anti-HER2 targeted therapies have proven to be a key treatment in the management of human epidermal growth receptor 2 (HER2)-positive breast cancers, as well as gastrointestinal tract tumors and head and neck tumors. Anti-HER2 therapies administered alone or in combination with chemotherapy have been extensively studied, but only limited robust data are available concerning the safety and efficacy of anti-HER2 molecules in combination with radiotherapy. *Methods:* We searched on Medline, Embase and Cochrane databases the articles providing data on the concomitant association between the antiHER2 therapies used in clinical practice (trastuzumab, pertuzumab, lapatinib and T-DM1) with radiotherapy. The articles were selected according to their pre-clinical and clinical relevance. *Results:* The trastuzumab-irradiation combination is the most studied, with a focus on the cardiac toxicity. The combination of lapatinib-irradiation was particularly studied in the context of cerebral metastases of HER2-positive breast cancer. The data on pertuzumab and T-DM1 were poor and are mainly case reports. *Conclusion:* To date, reliable conclusions about the toxicity and/or efficacy of concomitant irradiation with anti-HER2 therapies are difficult to make due to the heterogeneity of the data in the literature and need to be confirmed on a larger scale and long term follow-up. Nevertheless, no serious adverse events are reported and the toxicity profile seems to be manageable.
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The Human Epidermal growth Receptor 2 (HER2) is encoded by a proto-oncogene (*HER2/neu*) located on chromosome 17q21. The amplification of *HER2/neu* leads to the overexpression of HER2, a transmembrane receptor with intrinsic tyrosine kinase activity belonging to the Epidermal Growth Factor Receptor (EGFR). This overexpression is present in 15–30% of breast cancers and 21–33% of gastric or gastroesophageal junction cancers [1,2]. Receptor activation by dimerization or cleavage of its extracellular domain mediates proliferation signaling via the PI3K/Akt or MAP kinase pathways, enhancing cell growth, division and survival [3].

HER2 is therefore a relevant target because of its role in oncogenesis and tumor survival.

The HER2 status of a breast cancer or gastric cancer is defined on a tumor sample by immunohistochemistry (IHC) and/or FISH (fluorescence in situ hybridization) according to consensual criteria [4,5].

Various anti-HER2 molecules have been developed.

Trastuzumab was the first anti-HER2 molecule used in clinical practice. It is a humanized monoclonal antibody targeting the extracellular domain of HER2 (subdomain IV) that presents various mechanisms of action:

- Blocking of the proteolytic cleavage and dimerization of the receptor, thereby blocking the ligand-independent signaling and downstream signaling pathways (inhibition of PI3K-Akt and MAP kinase signaling pathways) [6,7].
- Stimulation of innate cellular immunity by recruiting natural killer cells and macrophages (ADCC) [8].

In clinical practice, trastuzumab is administered intravenously every 3 weeks (6 mg/kg after a first cycle of 8 mg/kg) or weekly (2 mg/kg after a first cycle of 4 mg/kg). Pharmacologically, the estimated half-life of trastuzumab is 28.5 days (Table 1) [9].

Trastuzumab is a key treatment in HER2-positive breast cancer. In the metastatic setting, Slamon et al. [10] compared first-line trastuzumab and chemotherapy to chemotherapy alone. Administration of trastuzumab increased mean overall survival (OS) from 20.3 months to 25.1 months ($p = 0.01$) and prolonged the time to

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Table 1
Half-life and dose of anti HER2 therapy.

	Half-life (days)	Dose (for adults)
Trastuzumab	28.5	*Breast cancer* Loading dose of 8 mg/kg IV followed by 6 mg/kg IV every 3 weeks or loading dose of 4 mg/kg IV followed by 2 mg/kg IV every week. *Gastric cancer* Loading dose of 4 mg/kg IV followed by 2 mg/kg IV weekly
Pertuzumab	18	Loading dose 840 mg IV, followed 3 weeks later by 420 mg IV every 3 weeks
T-DM1	3.5	3.6 mg/kg IV every 3 weeks
Lapatinib	1	1250 mg PO once daily on days 1–21 plus capecitabine (2000 mg/m^2/day PO, on days 1–14) in a repeating 21 day cycle

disease progression from 4.6 months to 7.4 months ($p < 0.001$) at median follow-up of 30 months. Similar results were subsequently reported in the adjuvant setting, such as in the HERA trial, in which absolute progression free survival (PFS) and OS at 23.6 months follow-up were improved by 6.3% (80.6% vs. 74.3%) and 2.7% (92.4% vs. 89.7%) in patients treated with and without trastuzumab for one year, respectively [11].

Since the ToGA trial, trastuzumab in combination with chemotherapy is also the standard treatment for patients with advanced HER2-positive gastric or gastroesophageal junction cancer, as this combination improved OS (hazard ratio HR 0.74; $p = 0.0046$) and PFS (HR 0.71; $p = 0.0002$). The adverse event profile was similar between the two arms, with no difference in the overall rate of adverse events (all grades or grade 3 or 4) [2].

Lapatinib is a tyrosine kinase inhibitor (TKI) that acts on the catalytic site of the tyrosine kinase domain in the intracellular domain of the HER2. It is a reversible inhibitor of HER1 and HER2 [12]. It inhibits cell proliferation by inhibition of the enzymatic activity (phosphorylation) of EGFR and/or HER2 and downstream effectors (PI3K/Akt/m-TOR and MAP kinase) [13]. In metastatic HER2-positive breast cancer, lapatinib added to capecitabine increases median PFS compared to capecitabine alone (8.4 vs 4.4 months, $p < 0.001$) beyond first metastatic line [14]. In another study in heavily pretreated patients, the trastuzumab-lapatinib combination increased OS and PFS (HR 0.74; $p = 0.026$ and HR 0.74; $p = 0.011$, respectively) [15]. Lapatinib is administered orally and has a half-life of 24 h after repeated dosing (Table 1) [16].

Pertuzumab is a recombinant humanized IgG antibody that prevents also dimerization of HER2 by binding to its extracellular portion (subdomain II). By blocking receptor dimerization, pertuzumab inhibits activation of HER2-dependent signaling pathways [17]. Pertuzumab is administered by intravenous infusion. At doses of 2 to 25 mg/kg, pertuzumab has linear pharmacokinetics with a median half-life of 18 days (Table 1). In the CLEOPATRA study, conducted in women with HER2-positive metastatic breast cancer, mean PFS was 18.5 months in the pertuzumab plus trastuzumab plus docetaxel arm versus 12.4 months in the placebo plus trastuzumab plus docetaxel arm (HR 0.62; $p < 0.0001$). OS was significantly improved in the pertuzumab arm (median OS: 56.5 months vs 40.8 months; HR 0.68; $p = 0.0002$) [18].

T-DM1 is another recent anti-HER2 therapy combining trastuzumab (T) with mertansine (DM1), a mitotic poison. Thanks to trastuzumab selectively binding to the HER2 receptor, T-DM1 is internalized by endocytosis. There follows a lysosomal degradation of the complex, leading to the release of DM1 within the HER2-positive cells. HER2 tumor cells are thus subjected to the same mechanism of action of trastuzumab alone, associated with the effects of DM1, leading to cell deaths by apoptosis [19]. T-DM1 improved OS (HR 0.68; $p < 0.001$) and PFS (HR 0.65; $p < 0.001$) compared to lapatinib plus capecitabine in the EMILIA trial. T-DM1 is indicated in the metastatic setting as second-line therapy after failure of pertuzumab-trastuzumab and docetaxel [20]. Similar results were reported in the TH3RESA trial compared to treatment left to the physician's discretion [21]. The median half-life was 3.5 days (Table 1) [22].

The main purpose of this review was to summarize published data on the toxicity and efficacy of all anti-HER2 therapies previously described, administered concomitantly with radiotherapy.

Methods

Search strategy

For this review, pre-clinical and clinical studies were identified through literature searches conducted from to January 1987 to December 2016. The search was performed using the National Library of Medicine (PubMed/MEDLINE), Excerpta Medical Database (EMBASE) and Cochrane database and only English written studies were selected. A research was performed using the following keywords "radiotherapy", "irradiation", "radiation", "concurrent", "concomitant" combined successively with each anti-HER2 therapy used in clinical practice ("trastuzumab", "pertuzumab", "lapatinib" and "T-DM1" or "trastuzumab emtansine"). Titles and abstracts of search results were screened to determine eligibility in the review.

Eligibility criteria

Concerning scientific studies, the following rules of selection were respected. The studies selected to explore the radioresistance due to HER2 receptor pathway had to demonstrate a particular biological mechanism. The work could have been carried out on all cell types, *in vivo* and *in vitro*, provided that the cells were HER2-positive. The articles that describe the radiosensitizing impact of the anti-HER2 therapies were focused on cancers treated in common practice (breast and stomach/esophagus cancers). Except for one article by Pietras et al. [25], studies using anti-HER2 agents not used in clinical practice were not included.

The clinical studies were selected according to their clinical relevance. Each study had to provide clinical data in terms of toxicity and/or efficacy concerning the concomitant association between the anti-HER2 agent (trastuzumab, pertuzumab, lapatinib and T-DM1) and irradiation. Concomitant irradiation was performed on the primary tumor site or secondary tumor sites. All radiotherapy modalities (standard fractionation, Stereotactic Radiosurgery (SRS)) were accepted and the irradiation protocol should be detailed.

Results

Overexpression HER2, a radioresistance factor

In preclinical studies *in vivo* and *in vitro*, it is clearly identified that HER2-overexpression is a factor of radioresistance in breast cancer [23–26]. An exogenously increase in HER2 levels in the MCF7 breast cancer cell line (which normally expresses low levels of HER2) by transfection (MCF7HER2) caused increased resistance of the cells to ionizing with increased clonogenic survival after radiation [23]. This radioresistance mechanisms are probably not all explored and complex.

However, it seems that the PI3-K/Akt pathway plays a major role. Its activation leads to resistance to apoptosis, deregulation of the cell cycle and acceleration of DNA repair mechanisms [23–26] This radioresistance can be also partly explained by a