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CADTH RAPID RESPONSE REPORT: SUMMARY OF ABSTRACTS

Combination Therapy for the Treatment of Adults with Any Stage Breast Cancer: Clinical Effectiveness and Guidelines

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Research Questions

1. What is the clinical effectiveness of combination therapy in adults with any stage of breast cancer?
2. What are the evidence-based guidelines associated with the use of combination therapy in adults with any stage of breast cancer?

Key Findings

Two systematic reviews (one with a meta-analysis), 15 non-randomized studies, and one evidence-based guideline were identified regarding combination therapy in adults with any stage of breast cancer.

Methods

A limited literature search was conducted on key resources including PubMed, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, randomized controlled trials, non-randomized studies and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and January 23, 2019. Internet links were provided, where available.

Selection Criteria

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults with breast cancer at any stage; including metastatic breast cancer
Interventions	The following interventions, either combined with each other (in groups of two or more) or combined with standard treatment options (conventional radiation therapy and/or chemotherapy): • Hyperbaric oxygen chamber therapy • UV blood irradiation (also known as extracorporeal photopheresis [ECP]) • Hyperthermia (any variant, including electric and magnetic) • Dendritic cell immunotherapy/immunization/vaccine • Autologous bone marrow stem cell transplant
Comparators	Q1: Any comparator; No comparator Q2: No comparator
Outcomes	Q1: Clinical effectiveness (e.g., progression-free survival, response rate, change in tumour size, overall survival, quality of life) and safety (e.g., toxicity, adverse events, discontinuation) Q2: Guidelines
Study Designs	Health technology assessments , systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, evidence-based guidelines

Results

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, non-randomized studies, and evidence-based guidelines.

Two systematic reviews (one with a meta-analysis), 15 non-randomized studies, and one evidence-based guideline were identified regarding combination therapy in adults with any stage of breast cancer. No relevant health technology assessments or randomized controlled trials were identified.

Additional references of potential interest are provided in the appendix.

Overall Summary of Findings

Two systematic reviews[1,2] (one with a meta-analysis[1]), 15 non-randomized studies[3-17], and one evidence-based guideline[18] were identified regarding combination therapy in adults with any stage of breast cancer. Detailed study characteristics are provided in Table 2.

When combining radiation therapy (RT) and hyperthermia (HT), the authors of the meta-analysis found that it enhanced the likelihood of complete response rates compared with RT alone.[1] Favourable outcomes of this combination were also highlighted by several non-randomized studies,[6,8-11] as well as its associated toxicity,[6,7,9,10] using a variety of comparators and sub-populations.

When combining chemotherapy and HT, one non-randomized study observed favourable results.[3]

When combining high dose chemotherapy (HDC) and autologous bone marrow or stem cell transplant, the authors of the one systematic review found that there was increased treatment-related mortality and little or no increase in survival.[2] However, this conflicts with non-randomized studies' findings.[12-17] Some highlight the benefits of this combination in very specific cancer subtypes or stages,[12-17] while another agrees with the lack of benefit.[16] The reader will note that the results of three non-randomized study publications[12-14] are drawn from the same data set, yet focus on different population subtypes.

When combining chemotherapy and immunotherapy, two non-randomized studies highlighted that dendritic cell and cytokine-induced killer cell (DC-CIK) immunotherapy can have favourable results in different sub-populations in the presence of a various chemotherapy agents and comparators.[4,5]

One evidence-based guideline was identified from the Deutsche Gesellschaft für Radioonkologie – DEGRO (German Society of Radiation Oncology).[18] This is an update to their 2012 interdisciplinary guidelines and focuses on therapies for locoregional breast cancer recurrences. Multiple modalities such as systemic therapy, surgery, radiation, and hyperthermia are discussed.[18]

Table 2: Summary of Included Studies

Author, Year	Study Characteristics; Intervention; Comparator	Outcomes	Results	Author Conclusions
Systematic Reviews and Meta-Analyses				
Datta, 2016[1]	N = 2,110; HT and RT, or HT and ReRT; RT alone, no comparator	CR	Overall, in comparative studies, a CR of 60.2% was achieved with RT + HT versus 38.1% with RT alone In single-arm studies, RT + HT attained a CR of 63.4% overall In studies looking at ReRT, a CR of 66.6% was achieved with HT and ReRT	"[HT] therapy enhances the likelihood of CR rates in [locally recurrent BCs] over RT alone by 22% with minimal acute and late morbidities. […] Thermoradiation therapy could therefore be considered as an effective and safe palliative treatment option for [locally recurrent BC]"[1]
Farquhar, 2016[2]	N = 5,600; HDC and autograft (bone marrow transplant or stem cell rescue); Chemotherapy alone	Survival rates; Toxicity; QoL	No increase to OS following HDC Treatment-related deaths were more frequent, and non-fatal morbidity was more common and more severe in HDC Worse QoL scores were reported immediately after HDC treatment, but were similar between the groups by one year	"There is high-quality evidence of increased treatment-related mortality and little or no increase in survival by using HDC with autograft for women with early poor prognosis [BC]."[2]
Non-Randomized Studies				
Klimanov, 2018[3]	N = 103; Combined chemotherapy and HT; Combined chemotherapy alone	Partial regression	Partial regression was achieved in 15.1% of the HT group and 4% in the control group	"The combined regional inductive moderate [HT] and chemotherapy treatment increased the overall therapeutic efficacy by 33.9% […]."[3]

Author, Year	Study Characteristics; Intervention; Comparator	Outcomes	Results	Author Conclusions
Lin, 2017[4]	N = 368; Low dose chemotherapy followed by DC-CIK immunotherapy Chemotherapy alone	Immune function; Disease-free survival; OS	Immune function is enhanced after the immunotherapy, OS is increased, and the risk of disease progression is reduced	"After low-dose chemotherapy, active immunization with DC-CIK immunotherapy is a potentially effective approach for the control of tumour growth in stage IV [BC] patients."[5]
Wang, 2016[5]	N = 23; Chemotherapy followed by DC-CIK immunotherapy; No comparator group	Progression-free survival; OS	Median progression-free survival was 13.5 months and OS was 15.2 months. Serious adverse events were neutropenia (100%), and anemia (69.7%)	"These data suggested that such combination therapy model be effective and safe for younger metastatic [triple-negative BC] exposure to previous anthracyclines and taxanes based adjuvant chemotherapy."[6]
Auoragh, 2016[6]	N = 18 participants (23 targets); Superficial brachytherapy with chemotherapy; Superficial brachytherapy with hyperthermia	Recurrence-free survival; DFS; OS; Side effects	At 5 years, recurrence-free survival was 56%, DFS was 28%, and OS was 22% Late side effects in 17% of patients, such as: fibrosis (11%) and chronic wound healing disorder (6%)	"[ReRT] as salvage brachytherapy with superficial [HT] for chest wall recurrences is a feasible and safe treatment with good local control results and acceptable late side effects."[7]
Oldenborg, 2016[7]	N = 234; ReRT and HT; No comparator	Occurrence of rib fractures	Rib fractures risk was 7% at 5 years	"The majority of rib fractures were located in the photon/electron abutment area, emphasizing the disadvantage of field overlap. […] Increasing the number of HT sessions a week does not increase the risk of rib fractures."[8]
Datta, 2015[8]	N = 24; HT and ReRT; No comparator	Response rates	Complete response in 66.7%, and partial response in 25% of patients At three years, the local control rate was 59.7%	"ReRT and HT is an effective and a safe modality to treat locoregional recurrences in previously irradiated [BCs]."[4]

Author, Year	Study Characteristics; Intervention; Comparator	Outcomes	Results	Author Conclusions
Linthorst, 2015[9]	N = 248; ReRT and HT; No comparator	CR; Local control; OS; Toxicity	CR rate was 70%. At 5 years, local control was 39% and OS was 18%. OS at 10 years was 10% Thermal burns in 23%, late grade 3 toxicity in 1%	"The combination of ReRT and HT results in a high rate of long-term [local control] with acceptable late toxicity, and many patients remained locally controlled for the rest of their survival period."[9]
Oldenborg, 2015[10]	N = 414; ReRT plus HT; No comparator group	Treatment response; Locoregional control; Prognostic factors for locoregional control and toxicity	Overall response rate was 86%. At three years, the locoregional control rate was 25%, and late grade toxicity was 23%	"ReRT+HT is an effective curative and palliative treatment option for patients with irresectable locoregional recurrent [BC] in previously irradiated area. […] The cumulative effects of past and present treatments should be accounted for by adjusting treatment protocol to minimize toxicity."[10]
Refaat, 2015[11]	N = 127 participants, 167 treatments sites; HT and RT; No comparator group	Treatment response; Local control; Survival	Greater OS was associated with greater radiation dose, HT dose, and local control Local control was 55.1% at last follow-up	"HT and RT rare effective for locally advanced or recurrent [BC] in patients that have been historically difficult to treat by RT alone. Over 50% of patients achieved control of locoregional disease. [OS] was improved with local control."[11]
Boudin, 2016[12]	N = 235; HDC and AHPCT; No comparator group	OS according to immunohistochemical subtype.	Median OS were 19.68 and 44.64 months for the triple negative and luminal subtypes respectively. There was no median OS for the HER2 subtype	"HDC-AHPCT does not change the prognostic value of [immunohistochemical] subtypes in MBC patients. OS favourably compares with data available in the literature on similar groups of patients."[12]

Author, Year	Study Characteristics; Intervention; Comparator	Outcomes	Results	Author Conclusions
Boudin, 2016[13]	N = 235; HDC and AHPCT; No comparator group	OS according to BRCA gene status (wild type or mutated)	Presence of the BRCA gene mutation was a prognostic factor for OS and PFS	"In this large series of MBC receiving HDC-AHPCT, we report a highly favorable survival outcome in the subset of patients with documented germline BRCA mutations."[13]
Boudin, 2016[14]	N = 67; HDC and AHPCT; No comparator group	OS according to immunohistochemical subtype.	OS at five years were 57% and 89% for the triple negative and HER2 subtypes respectively	"In [inflammatory breast cancer] patients receiving HDC-AHPCT, OS favorably compares with data available in the literature on similar groups of patients."[14]
Martino, 2016[15]	N = 583; HDC and autologous hematopoietic stem cell transplantation; No comparator group	Toxicity; Efficacy	Overall transplant-related mortality was 1.9% OS at five and 10 years was 75% and 64% respectively. For the same periods, disease free survival was 58% and 44%	"Adjuvant HDC with [autologous hematopoietic stem cell transplantation] has a low mortality rate and provides impressive long-term survival rates in patients with high-risk BC."[15]
Hamilton, 2015[16]	N = 285 HDC and autologous hematopoietic cell transplantation; No comparator group	Long-term clinical results	There were 34 long-term survivors, the majority of which had primary or recurrent oligometastatic disease	"This retrospective evaluation of patients who underwent [autologous hematopoietic cell transplantation] for MBC demonstrates long-term survival in a small subset of patients, primarily those with primary or recurrent oligometastatic disease. […] We thus conclude there remains no overall-survival benefit to HDC in MBC."[16]

Author, Year	Study Characteristics; Intervention; Comparator	Outcomes	Results	Author Conclusions
Pedrazzoli, 2014[17]	N = 1,183 HDC and AHPCT; No comparator group	Toxicity; Efficacy	Transplantation-related mortality was 0.8%, late cardiac and secondary tumour-related were ~1% Median disease-free survival was 101 months, and median OS was 134 months	"Adjuvant HDC with AHPCT has a low mortality rate and provides impressive long-term survival rates in patients with high-risk primary BC."[17]
Evidence-Based Guideline				
Harms, 2016[18]	Patients with locoregional breast cancer recurrences; Multiple modalities NA	NA	NA	"Following primary mastectomy, patients with resectable locoregional breast cancer recurrences should receive multimodality therapy including systemic therapy, surgery, and radiation [with or without] hyperthermia. This approach results in high local control rates and long-term survival is achieved in a subset of patients."[18]

AHPCT = autologous hematopoietic progenitor cell transplantation; BC = breast cancer CR = complete response; DC-CIK = dendritic cell and cytokine-induced killer cell; DFS = disease-free survival; HDC = high dose chemotherapy; HT = hyperthermia; MBC = metastatic breast cancer; NA = not applicable; OS = overall survival; QoL = quality of life; ReRT = reirradiation; RT = radiation therapy.

References Summarized

Health Technology Assessments

No literature identified.

Systematic Reviews and Meta-analyses

Radiation and Hyperthermia

1. Datta NR, Puric E, Klingbiel D, Gomez S, Bodis S. Hyperthermia and radiation herapy in locoregional recurrent breast cancers: a systematic review and meta-analysis. *Int J Radiat Oncol Biol Phys*. 2016 Apr 1;94(5):1073-1087. PubMed: PM26899950

Chemotherapy and Autologous Bone Marrow/Stem Cell Transplantation

2. Farquhar C, Marjoribanks J, Lethaby A, Azhar M. High-dose chemotherapy and autologous bone marrow or stem cell transplantation versus conventional chemotherapy for women with early poor prognosis breast cancer. *Cochrane Database Syst Rev*. 2016 May 20(5):Cd003139.
PubMed: PM27200512

Randomized Controlled Trials

No literature identified.

Non-Randomized Studies

Chemotherapy and Hyperthermia

3. Klimanov MY, Syvak LA, Orel VE, et al. Efficacy of combined regional inductive moderate hyperthermia and chemotherapy in patients with multiple liver metastases from breast cancer. *Technol Cancer Res Treat*. 2018 Jan 1;17:1533033818806003.
PubMed: PM30336769

Chemotherapy and Immunotherapy

4. Lin M, Liang S, Jiang F, et al. 2003-2013, a valuable study: Autologous tumor lysate-pulsed dendritic cell immunotherapy with cytokine-induced killer cells improves survival in stage IV breast cancer. *Immunol Lett*. 2017 Mar;183:37-43.
PubMed: PM28143792

5. Wang X, Ren J, Zhang J, et al. Prospective study of cyclophosphamide, thiotepa, carboplatin combined with adoptive DC-CIK followed by metronomic cyclophosphamide therapy as salvage treatment for triple negative metastatic breast cancers patients (aged <45). *Clin Transl Oncol*. 2016 Jan;18(1):82-87.
PubMed: PM26266766

Radiation and Hyperthermia

6. Auoragh A, Strnad V, Ott OJ, Beckmann MW, Fietkau R. Re-irradiation of the chest wall for local breast cancer recurrence : Results of salvage brachytherapy with hyperthermia. *Strahlenther Onkol*. 2016 Sep;192(9):617-623.
PubMed: PM27381751

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PubMed: PM26856858

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PubMed: PM25906357

9. Linthorst M, Baaijens M, Wiggenraad R, et al. Local control rate after the combination of re-irradiation and hyperthermia for irresectable recurrent breast cancer: Results in 248 patients. *Radiother Oncol*. 2015 Nov;117(2):217-222.
PubMed: PM26002305

10. Oldenborg S, Griesdoorn V, van Os R, et al. Reirradiation and hyperthermia for irresectable locoregional recurrent breast cancer in previously irradiated area: Size matters. *Radiother Oncol*. 2015 Nov;117(2):223-228.
PubMed: PM26542015

11. Refaat T, Sachdev S, Sathiaseelan V, et al. Hyperthermia and radiation therapy for locally advanced or recurrent breast cancer. *Breast (Edinburgh, Scotland)*. 2015 Aug;24(4):418-425.
PubMed: PM25900383

Chemotherapy and Autologous Stem Cell Transplantation

12. Boudin L, Chabannon C, Sfumato P, et al. Immunohistochemical subtypes predict survival in metastatic breast cancer receiving high-dose chemotherapy with autologous haematopoietic stem cell transplantation. *Eur J Cancer*. 2016 Apr;57:118-126.
PubMed: PM26918737

13. Boudin L, Goncalves A, Sabatier R, et al. Highly favorable outcome in BRCA-mutated metastatic breast cancer patients receiving high-dose chemotherapy and autologous hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2016 Aug;51(8):1082-1086.
PubMed: PM27042835

14. Boudin L, Goncalves A, Sfumato P, et al. Prognostic impact of hormone receptor- and HER2-defined subtypes in inflammatory breast cancer treated with high-dose chemotherapy: a retrospective study. *J Cancer*. 2016;7(14):2077-2084.
PubMed: PM27877223

15. Martino M, Lanza F, Pavesi L, et al. High-dose chemotherapy and autologous hematopoietic stem cell transplantation as adjuvant treatment in high-risk breast cancer: data from the european group for blood and marrow transplantation registry. *Biol Blood Marrow Transplant*. 2016 Mar;22(3):475-481.
PubMed: PM26723932

16. Hamilton BK, Rybicki L, Abounader D, et al. Long-term survival after high-dose chemotherapy with autologous hematopoietic cell transplantation in metastatic breast cancer. *Hematol Oncol Stem Cell Ther*. 2015 Sep;8(3):115-124.
PubMed: PM26183670

17. Pedrazzoli P, Martinelli G, Gianni AM, et al. Adjuvant high-dose chemotherapy with autologous hematopoietic stem cell support for high-risk primary breast cancer: results from the Italian national registry. *Biol Blood Marrow Transplant*. 2014 Apr;20(4):501-506.
PubMed: PM24374214

Guidelines and Recommendations

18. Harms W, Budach W, Dunst J, et al. DEGRO practical guidelines for radiotherapy of breast cancer VI: therapy of locoregional breast cancer recurrences. *Strahlenther Onkol*. 2016 Apr;192(4):199-208.
PubMed: PM26931319

Appendix — Further Information

Systematic Reviews and Meta-analyses

Alternative Population – Mixed Cancers

19. Zhou H, Wu W, Tang X, Zhou J, Shen Y. Effect of hyperthermic intrathoracic chemotherapy (HITHOC) on the malignant pleural effusion: A systematic review and meta-analysis. *Medicine (Baltimore)*. 2017 Jan;96(1):e5532.
PubMed: PM28072694

Randomized Controlled Trials

Radiation and Hyperthermia

Alternative Population – Type of Cancer Unclear

20. Chi MS, Yang KL, Chang YC, et al. Comparing the effectiveness of combined external beam radiation and hyperthermia versus external beam radiation alone in treating patients with painful bony metastases: a phase 3 prospective, randomized, controlled trial. *Int J Radiat Oncol Biol Phys*. 2018 Jan 1;100(1):78-87.
PubMed: PM29066122

Non-Randomized Studies

Alternative Population – Other Cancers or Mixed Cancers

Chemotherapy and Hyperthermia

21. Ranieri G, Ferrari C, Di Palo A, et al. Bevacizumab-based chemotherapy combined with regional deep capacitive hyperthermia in metastatic cancer patients: a pilot study. *Int J Mol Sci*. 2017 Jul 6;18(7).
PubMed: PM28684680

Review Articles

22. Kouloulias V, Triantopoulou S, Uzunoglou N, et al. Hyperthermia is now included in the NCCN clinical practice guidelines for breast cancer recurrences: an analysis of existing data. *Breast care (Basel, Switzerland)*. 2015 Apr;10(2):109-116.
PubMed: PM26195939