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Research Article

COMPARATIVE EVALUATION BETWEEN QUALITY OF LIFE (QoL), ADVERSE EVENTS AND SURVIVAL ANALYSIS OF MISTLETOE EXTRACT FOR THE TREATMENT OF SOLID TUMORS.

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ABSTRACT

Objective: Mistletoe extract such as Iscador generally used for the treatment of various type of cancers, specifically solid cancers. It was obtained from *viscum album*. Objective: The present investigation was carried to find out the comparative evaluation of Quality of life (Qol), adverse events and survival analysis of mistletoe extract for the treatment of solid cancers in data published since 2001.

Methods: A comprehensive in depth search was conducted on following search engines: Pubmed and Google using the following Medical Subject Headings (MeSH) and key words in the database search: "Randomized controlled trial", "iscador", "Cancer", "Mistletoe preparation", "*Viscum album*" till April 2013. Only reports fulfilling the inclusion criteria were included in the data analysis. The search was limited to human studies, clinical trials, and English language studies. Outcome data extracted from publications as they are given.

Results: 76 publications found initially, screening of these results yielded 40 studies and remaining studies were excluded due to non-compliance with inclusion criteria. Thereafter 31 studies excluded due to insufficient data for analysis. At last 9 studies were included in the present comparative evaluation.

Conclusion: Comparative evaluation finds that Qol in cancer patients was measured by European Organization for Research and Treatment of Cancer (EORTC), Quality of Life-score 30 (QLQ-C30), Functional living index cancer (FLIC), Traditional Chinese medicine index (TCMI), karnofsky performance index (KPI), GLQ-8 and Spitzer's uniscale. In all studies adverse events related to mistletoe extract treatment were local reaction at the injection site, chill and muscle pain, allergic skin reaction and fever. Survival analysis done by using Wilcoxon paired sample test and cox proportion hazard model and hazard ratio was reported to 0.36 to 1.32.

Keywords: Mistletoe extract, solid tumors, adverse events, quality of life and survival analysis.

INTRODUCTION

Among the complementary therapeutic strategies used in oncology, the aqueous extracts of European mistletoe (*Viscum album* L.), or Iscsador are the most frequently used medications. It has been employed in the treatment of uterine, gastric, head and neck and cervical cancer. The reports regarding the efficacy of the treatment are varied and mistletoe preparations are used either alone or combined with other alternative medical methods. Aqueous mistletoe extracts (*Viscum album* L.) have been extensively used in complementary cancer therapy. Mistletoe extracts as well as isolated mistletoe-lectins have been indicated to have immunomodulatory properties by bolstering the secretion of cytokines and the number and activity of immunological effector cells like NK-cells and T lymphocytes (Büssing *et al*., 1999; Schink *et al*., 2006; Huber *et al*., 2011).

It has been shown in clinical trials, especially with breast or colorectal cancer patients that QoL improved under mistletoe therapy (Horneber *et al*., 2008). However, there is paucity of recent systematic reviews to elucidate the clinical trials of mistletoe extract. Hence, the objective of the present review was to discern the therapeutic landscape of mistletoe extract by appraising the investigations of mistletoe extract.

METHODS

A comprehensive in depth search was conducted on following search engines: Pubmed and Google using the following Medical Subject Headings (MeSH) and key words in the database search: "Randomized controlled trial", "iscador", "Cancer", "Mistletoe preparation", "*Viscum album*" till April 2013. Only reports fulfilling the inclusion criteria were included in the data analysis. The search was limited to human studies, clinical trials, and English language studies.

Inclusion criteria

- Published studies where mistletoe extract or Iscador used treatment of solid tumors.
- Published studies in which randomization used
- Studies published on and after year 2001.
- Exclusion criteria:
- Publications in which mistletoe extract or Iscador or *Viscum album* not used as a treatment.
- Publications in which animal or *in vitro* studies conducted.
- Publications available in other than English language.

RESULTS

Initially 76 articles were identified by computerized search of databases and from these, 36 studies were excluded by examination of their titles. Excluded studies were mainly duplicates, studies, and study designs other than randomized controlled trials, studies on animals and studies published in languages other than English. Remaining 31 studies excluded due to insufficient data for analysis. From this process, a total of 9 articles were potentially eligible. Identification of relevant studies is detailed in Fig. 1

Study characteristics and results

The nine trials were fulfilled the above criteria and thus included in the study.

Semiglazov*et al*., (2006) conducted a randomised, multicentre, double-blind clinical trial of PS76A2, an aqueous mistletoe extract

standardized to mistletoe lectins in breast cancer patients. 352 patients were randomly allocated to 2 groups receiving PS76A2 (15 ng mistletoe lectin/0.5 ml) or matching placebo twice weekly for 4 to 6 cycles of CMF (cyclophosphamide, methotrexate, fluorouracil) chemotherapy followed by 2 months follow-up. Quality of life was measured by FACT-G scale, GLQ-8 and pitzer's uniscale. The total score increased by 4.40±11.28, 28.9 ± 154.6 and 12.2±30.7 with respective FACT-G scale, GLQ-8 and pitzer's scaleindicating a higher QoL after PS76A2, however Qol was significantly(P<0.0001) decreased by placebo. After follow-up without chemotherapy, a significant treatment difference in favour of PS76A2 was determined by means of FACT-G, GLQ-8 and Spitzer's uniscale. PS76A2 was well tolerated in this trial, with the exception of adverse events related to treatment such as reddening of skin, allergic skin reaction, adverse related to chemotherapy and adverse events related to chemotherapy predominantly of the hematological and gastrointestinal system. In conclusion, during chemotherapy and follow-up of breast cancer patientsPS76A2 was shown to be safe and effective in improving QoL.

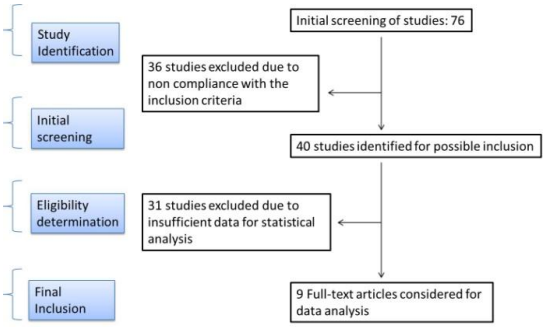

Fig.1: Process of selecting articles for inclusion in the review.

Piao *et al*., (2004) performed multicentric, prospective, randomized clinical trial in China. 224 cancer patients (breast, ovarian and non-small lung cancer) were selected for final analysis. In that n=115 treated with HELIXOR and n=109 were treated with approved immunomodulating phytopharmacon Lentinan (control). Quality of Life was measured using FLIC, TCMI and KPI. QoL was significantly (P< 0.05) improved in patients who were administered only HELIXOR, when compared with its control. Adverse events (AE) were found to fever, pruritus at the injection and local inflammatory skin reaction at the subcutaneous injection site. AE occurred less frequent in HELIXOR when compared with control group. In conclusion, treatment with HELIXOR significantly improves QoL and decreases adverse events.

Kim *et al*., (2012) carried out a randomized controlled trial of gastric cancer patients. 32 operated gastric cancer patients were randomized into doxifluridine group and control group with additional therapy with aVQ or no additional therapy. aVQ was injected subcutaneously three times per week from postoperative day 7 to week 24 in increasing doses. Adverse events such as post-operative bleeding, an acute infection, injection site like local pain, itching, rash or urticarial, chest pain, 1 case of myalgia, 1 case of dizziness and and 1 case of diarrhea were reported in treatment group and control group. Global health status (P< 0.01), leukocyte and eosinophil counts (P≤0.01) increased significantly in the treatment group compared to the control group. Diarrhea was less frequently reported (7% vs. 50%, P=0.014) in the intervention group. There was no significant treatment effect on levels of TNF-alpha, IL-2, $CD16^+/CD56^+$and CD 19^+ lymphocytes and liver function tests. In conclusion, additional therapy with aVQ significantly improves QoL of gastric cancer patients.

Semiglazov *et al*., (2004) conducted a placebo-controlled trial. 272 patients with breastcancer receiving adjuvant CMF chemotherapy were enrolled and randomised to two groups, receiving placebo or PS76A2 at concentrations of 10, 30 or 70 ng mistletoe lectin (ML) per ml. As a result, statistically significant effects on QoL were obtained with the medium dose (15 ng ML/0.5 ml). The results on QoL were supported by an increase of T helper lymphocytes (CD4+) and the CD4+/CD8+ ratio (P<0.05). Various adverse events were reported such as local reaction at the injection site, chill and muscle pain, allergic skin reaction, allergic conjunctivitis, headache, white cell and reticulo-endothelial system disorders, gastro-intestinal system disorders, resistance mechanism disorders, red bloodcell disorders. In conclusion, the medium dose of PS76A2 (15 ng ML/0.5 ml twice weekly) was significantly improved QoL in breast cancer patients.

Steuer-Vogt *et al*., (2001) reported a prospective, randomized controlled clinical trial involving 477 patients with head and neck squamous cell carcinoma. Then patients were stratified into two treatment groups that underwent surgery or surgery followed by radiotherapy and both groups were randomized for additional treatment with mistletoe extract. No improvement in QoL was observed. Adverse events found to be rubor and prurigo, induration, vesiculation. In conclusion, mistletoe preparation did not show any adjuvant indication in the head and neck squamous cell carcinoma patients.

Grossarth-maticek and ziegler, (2008) reported a four controlled cohort studies. In which, two randomized matched-pairs studies: corpus uteri cancer patients without (30 pairs) and with distant metastases (26 pairs) that never used any kind of mistletoe therapy were matched for prognostic factors.Two non-randomized matched-pairs studies: corpus uteri cancer patients without (103 pairs) and with distant metastases (95 pairs) that already received mistletoe (Iscador) therapy were matched by the same criteria to control patients without mistletoe extract therapy.

Significant effect in favor of mistletoe extract therapy was found in randomized study, non-randomized showed no evidence for an effect: estimate of the hazard ratio and 95% confidence interval: 0.36 (0.16, 0.82) and 1.00 (0.46, 2.16) respectively. In conclusion, the mistletoe preparation has the effect of prolonging overall survival of corpus uteri cancer patients.

Grossarth-maticek and ziegler, (2007) reported a four controlled cohort studies. In that, two randomized and two non-randomized matched pair studies. Two randomized matched-pair studies: *OvarRand* (ovarian cancer patients without distant metastases; 21 pairs) and *OvarMetRand* (ovarian cancer patients with distant metastases; 20 pairs); patients having no mistletoe therapy were matched for prognostic factors. Two non-randomized matched-pair studies: *Ovar* (ovarian cancer patients without distant metastases; 75 pairs) and *OvarRand* (ovarian cancer patients with distant metastases; 62 pairs); patients that already received therapy with mistletoe extracts were matched by the same criteria to control patients without therapy with mistletoe extracts. In randomized studies, overall survival favors Iscador, *OvarMetRand* and *OvarRand;* hazard ratio estimate and 95 % confidence interval: 0.40 (0.15, 1.03) and 0.33 (0.12, 0.92), respectively. In conclusion, mistletoe extracts prolonged overall survival of ovarian cancer patients.

Grossarth-maticek and ziegler, (2006) reported a randomized matched-pairs study and non-randomized matched-pairs studies. Iscador therapy on overall survival is significantly favors in both randomized and non-randomized trials. Estimate of hazard ratio and 95 % confidence interval in breast cancer with local recurrences and no metastases 0.52 (0.23, 1.17); breast cancer with lymphatic metastases: 0.27 (0.15, 0.50); breast cancer with distant metastases: 0.53 (0.32, 0.88). In conclusion, overall survival in patients receiving mistletoe treatment is longer.

Kleeberg *et al*., (2003) performed a randomized phase III trial to estimate effectiveness of rIFN-α2b or rIFN-γ with control group. Another arm Iscador was added. The hazard ratio estimates (95% confidence intervals (CI)) were 1.04 (0.84, 1.30) for the comparison of rIFN-a2b versus control, 0.96 (0.77, 1.20) for rIFN-g versus control, and 1.32 (0.93, 1.87) for Iscador versus control. In conclusion, results showed no clinical benefit for adjuvant treatment with low dose rIFN-a2b or rIFN-g or with Iscador in high-risk melanoma patients.

Table No: 1 Adverse Event of included studies

S. No	Author name	Type of cancer	Study design	ADR related to mistletoe extract	ADR related to other therapy
1.	Semiglazov *et al*., 2006	Breast cancer	Randomized, double blind	Reddening of skin, and allergic skin reaction, in one patient acute otitis, adverse related to chemotherapy	Related to haematological, chemotherapy and gastrointestinal system
2.	Piao *et al*., 2004	Breast, ovarian and Non-small lung cancer	Randomized clinical trial	Fever, pruritus at the injection and local inflammatory skin reaction at the subcutaneous injection site.	Related to chemotherapy
3.	Kim *et al*., 2012	Gastric carcinoma	Randomized, controlled	post-operative bleeding, an acute infection, injection site like local pain, itching, rash or urticarial, chest pain, 1 case of myalgia, 1 case of dizziness and and 1 case of diarrhea.	Diarrhea.
4.	Semiglazov *et al*., 2004	Breast cancer	Randomized, double blind, placebo controlled	local reaction at the injection site, chill and muscle pain, allergic skin reaction, allergic conjunctivitis, headache, white cell and reticulo-endothelial system disorders, gastro-intestinal system disorders, resistance mechanism disorders, red blood cell disorders	white cell and reticulo-endothelial system disorders, gastro-intestinal system disorders, resistance mechanism disorders, red blood cell disorders
5.	Steuer-Vogt *et al*., 2001	Head and neck squamous cell carcinoma.	prospective, randomised controlled clinical trial	rubor and prurigo, induration, Vesiculation,	-------

Table 2: Quality Of Life of included studies

S. No	Author name	Type of cancer	Study design	Qol	Medication
1	Semiglazov *et al*., 2006	Breast cancer	Randomized, double blind	Measured by - primary outcome variable - FACT-G scale; secondary outcome variables - GLQ-8 (Global Quality of Life Scale) and Spitzer's uniscale	PS76A2, an aqueous mistletoe extract standardised to mistletoe Lectins
2.	Piao *et al*., 2004	Breast cancer	Randomized clinical trial	Measured by FLIC, TCMI and KPI	HELIXOR – standardized mistletoe extract
3.	Kim *et al*., 2012	Gastric carcinoma	Randomized, controlled	EORTC QLQ-C30 and -STO22	AbnobaVISCUMW Q 20 mg
4.	Semiglazov *et al*., 2004	Breast cancer	Randomised, placebo-controlled	GLQ-8 and Spitzer's uniscale.	Lektinol(aqueous mistletoe extract) subcutaneously
5.	Steuer-Vogt *et al*., 2001	Head and neck squamous cell carcinoma.	Randomised controlled clinical trial	(EORTC) Quality of Life-score 30 (QLQ-C30)	Subcutaneous (s.c.) injections of a mistletoe extract (Eurixor1, biosyn)

Table 3: Survival Analysis of included studies

S. No	Author name	Type of cancer	Study design	No of patients	Survival analysis done by	Hazard ratio
1.	Grossarth-maticek and ziegler, 2008	Corpus uteri cancer	Randomized and non-randomized prospective controlled	254 pairs	Wilcoxon paired sample test and cox proportion hazard model	0.36 (0.16, 0.82)

2.	Grossarth-maticek and ziegler, 2007	Ovarian cancer	Randomized and non-randomized prospective controlled	178 pairs	Wilcoxon paired sample test and cox proportion hazard model	0.40 (0.15, 1.03)
3.	Grossarth-maticek and ziegler, 2008	Breast cancer	Randomized and non-randomized prospective controlled	197 pairs	Cox proportional hazard regression model	0.52 (0.23, 1.17)
4.	Kleeberg et al., 2003	Melanoma	Prospective, randomised phase III adjuvant trial	830 patients	Cox proportional hazard regression model	1.32 (0.93, 1.87)

DISCUSSION

Viscum album L. extracts (VAE or European mistletoe constitute a frequently used plant extract employed to treat across an array of cancerous lesions or manifestations especially in gynecological and breast-cancer treatment (Fasching, 2007; Molassiotis et al., 2006; Molassiotis et al., 2005). *Viscum album,* a hemi-parasitic shrub and bears an array of bioactive moieties. Mistletoe lectins (ML I, II and III) have been most widely studied. MLs consist of two polypeptide chains: a carbohydrate-binding B-chain that can bind on cell surface receptors, which enables the protein to enter the cell and the catalytic A-chain which can subsequently inhibit protein synthesis, due to its ribosome-inactivating properties, by removing an adenine residue from the 28S RNA of the 60S subunit of the ribosome (Endo, 1988; Stirpe, 1982; Stirpe, 1992). Whole VAE as well as several of the compounds are cytotoxic and the MLs in particular have strong apoptosis-inducing effects (Eggenschwiler, 2007; Bussing 1999; Elsässer-Beile, 1998). Breast and gynecological cancers (*i.e.* ovarian, endometrial, cervical, vaginal, vulval, and fallopian cancers) account for a significant amount of morbidity and mortality in women.

A plethora of clinical studies and experiments have elucidated the potential therapeutic effects of VAE and its compounds in breast and gynecological cancer, and indicating positive effects. The major contributors to the clinical efficacy are the improvement in the quality of life and the tolerability of conventional treatment. Quality of life improvement in breast cancer was reported by Semiglazov *et al*., 2006, who employed FACT-G scale, GLQ-8 and Spitzer's uniscale. A couple of other authors also reported similar results in breast cancer patients employing FLIC, TCMI and KPI (Piao *et al*., 2004) and GLQ-8 and Spitzer's uniscale (Semiglazov *et al*., 2004). The effect of mistletoe extract was reported by Kim *et al*., (2012) and Steuer-Vogt *et al*., (2001) in the treatment of gastric and head and neck carcinoma respectively. They employed the EORTC QLQ-C30 and -STO22 and (EORTC) Quality of Life-score 30 (QLQ-C30) scores respectively. Most of the studies demonstrate that various quality of life instruments have been employed in the measurement of the quality of life of the patients of cancer and mistletoe extract was able to ameliorate the symptomatology of the cancer patients. However, the study by Steuer-Vogt et al., (2001) demonstrated that the 5-year survival rates of patients from the mistletoe group were no better than the survival rates of patients from the control group. Furthermore, no significant changes in the in quality of life could be detected. It was concluded that mistletoe preparation had no direct alleviating impact in the adjuvant treatment of patients with head and neck cancer.

Survival analysis was employed by a number of authors to determine the efficacy of mistletoe extract in treatment of various types of cancer. Wilcoxon paired sample test and cox proportion hazard model was employed by Grossarth-maticek and ziegler, 2008; Grossarth-maticek and ziegler, 2007 whereas Cox proportional hazard regression model was employed by Grossarth-maticek and ziegler, 2008 and Kleeberg *et al*., 2003.

The study by Grossarth-maticek and ziegler, 2006, 2007 and 2008 demonstrated that mistletoe extract has the effect of prolonging overall survival of breast, ovarian and corpus uteri cancer patients respectively. However, the results of show no clinical benefit for

adjuvant treatment with low dose rIFN- α2b or rIFN-γ or with Iscador M@ in high-risk melanoma patients (Kleeberg *et al*., 2003).

Various side effects have been recorded by investigators which encompass a number of organ systems. Reddening of skin, and allergic skin reaction, in one patient acute otitis, adverse related to chemotherapy was reported by Semiglazov *et al*., 2006. Piao *et al*., 2004 reported Fever, pruritus at the injection and local inflammatory skin reaction at the subcutaneous injection site. post-operative bleeding, an acute infection, injection site like local pain, itching, rash or urticarial, chest pain was reported by Kim *et al*., 2012. Semiglazov *et al*., 2004 reported local reaction at the injection site, chill and muscle pain, allergic skin reaction, allergic conjunctivitis, headache, white cell and reticulo-endothelial system disorders, gastro-intestinal system disorders, resistance mechanism disorders, red blood cell disorders. rubor and prurigo, induration, Vesiculation, was reported by Steuer-Vogt *et al*., 2001.

The analysis of pooled data from the clinical trials demonstrates that adjuvant treatment of cancer patients with mistletoe extract provides a better chance of survival to patients. Transparent design and clear endpoints will be needed in the forthcoming trials to enable us to unravel hidden properties

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