proceedings

MDPI

Proceedings

Lentinan for Integrative Cancer Treatment: An Umbrella Review †

Michele Antonelli [1,*], Davide Donelli [2] and Fabio Firenzuoli [3]

[1] Public Health Service, AUSL-IRCCS Reggio Emilia, via Giovanni Amendola 2, 42122 Reggio Emilia, Italy
[2] Primary Care Service, AUSL-IRCCS Reggio Emilia, 42122 Reggio Emilia, Italy; donelli.davide@gmail.com
[3] CERFIT, Careggi University Hospital, 50134 Florence, Italy; fabio.firenzuoli@unifi.it
* Correspondence: to: michele.antonelli@ausl.re.it
† Presented at the 1st International Electronic Conference on Biomolecules: Natural and Bio-Inspired Therapeutics for Human Diseases, 1–13 December 2020; Available online: https://iecbm2020.sciforum.net/.

Abstract: The aim of this review is to understand whether lentinan can be a useful integrative remedy for cancer patients. PubMed, EMBASE, Web of Science, Cochrane Library and Google Scholar were screened for relevant meta-analyses from inception to 29th September 2020. After database search, 8 meta-analyses met inclusion criteria. Retrieved evidence reported that lentinan may be useful to improve response rate, 1-year survival, performance status, quality of life and radio/chemotherapy toxicity when administered in adjunct to standard therapy, especially for some lung and gastrointestinal cancers. Further studies are advised due to limitations of existing evidence.

Keywords: lentinan; lentinula edodes; shiitake; cancer; integrative therapy; review

Citation: Antonelli, M.; Donelli, D.; Firenzuoli, F. Lentinan for Integrative Cancer Treatment: An Umbrella Review. *Proceedings* **2021**, *79*, 1. https://doi.org/10.3390/IECBM2020-08733

Published: 1 December 2020

1. Introduction

Lentinan is a polysaccharide isolated from *Lentinula edodes* (also called "shiitake" in Japanese), an edible mushroom traditionally used in Asian medicine for the treatment of various ailments, such as infectious and oncologic diseases [1]. In particular, from a chemical point of view, lentinan is a beta-(1,3)-glucan with beta-(1,6) branches characterized by a molecular weight of 1153 g/mol [2]. As reported by the Memorial Sloan Kettering Cancer Center, purported traditional uses of lentinan include cancer treatment and prevention, cholesterol lowering effects, immune system boosting and infection control [3]. Qualitative reviews of laboratory and clinical studies suggested that lentinan can enhance some immune functions and improve response rates, performance status, quality of life and chemotherapy-related adverse effects if administered in adjunct to standard therapy in patients with various cancer types, mostly lung, gastric and colorectal tumors [1,2,4,5].

Research Aim

The aim of this umbrella review is to understand whether lentinan can be a useful integrative remedy for cancer patients on the basis of quantitative evidence from existing meta-analyses of clinical studies.

2. Methods

This research work was designed as an umbrella review of the scientific literature [6]. All relevant meta-analyses investigating the efficacy of lentinan supplementation for integrative cancer treatment were included. No publication date or language restrictions were posed. The following PICOS criteria (Population, Intervention, Comparison, Outcomes, Study design) were applied for the inclusion and exclusion of screened articles:

- P (population): patients diagnosed with any type of cancer disease.
- I (intervention): the administration of lentinan in adjunct to standard care.
- C (comparison): standard care only or standard care plus placebo.

- O (outcomes): any validated outcome measurement to evaluate potential health-related improvements (response rate, survival rate, performance status, quality of life and any decrease in radio- or chemo-therapy toxicity).
- S (study design): meta-analyses of clinical studies.

In view of shared recommendations about optimal database combinations for literature searches [7], PubMed, EMBASE, Web of Science, Cochrane Library and Google Scholar were systematically screened for relevant articles. All databases were searched from inception to 29th September 2020. The following keywords were used: "lentinan", "*Lentinula edodes*", "*Lentinus edodes*", "shiitake", "cancer", and "tumor". Proper Boolean operators and database filters were applied to optimize the search. For example, in PubMed, this search strategy was applied: *("Lentinula edodes"[Title/Abstract] OR "Lentinus edodes"[Title/Abstract] OR lentinan[Title/Abstract] OR shiitake[Title/Abstract]) AND (cancer[Title/Abstract] OR tumor[Title/Abstract]).* Filters applied: Meta-Analysis, Review, Systematic Review.

The quality of included studies was evaluated with a validated assessment tool designed by the National Institutes of Health (NIH) [8]. Meta-analyses were assessed individually and their overall quality, ranging from a minimum of 0 to a maximum of 8, was rated as "poor" (C) if 3 or less items were positive, "fair" (B) if 4 or 5 items were positive and "good" (A) if at least 6 items were positive. Results of the overall quality assessment were reported in a specific column of Table 1. After article selection, relevant data (characteristics of intervention, control type, analyzed outcomes and results of included meta-analysis) were manually extracted. Then, retrieved evidence was summarized and briefly discussed.

3. Results

From the database search, 430 articles were found (PubMed: 34; EMBASE: 30; Web of Science: 28; Cochrane Library: 0; Google Scholar: 338) and 8 meta-analyses met inclusion criteria [9–16]. In particular, three studies were network meta-analyses [9,10,12], whereas the other included research works were standard meta-analyses. The number of clinical studies about lentinan efficacy included in each meta-analysis largely varied, thus, ranging from 1 to 65.

Intervention was defined as the administration of lentinan in adjunct to chemotherapy and, in one case, to radiotherapy [9]. Control groups received standard care alone. During each therapeutic session, lentinan was usually administered intravenously at a dose of 1 mg [9,10,12]. In general, the weekly dose did not exceed 2 mg [11]. The treatment course lasted, on average, from 2 to 8 weeks [15]. In one meta-analysis investigating the efficacy of lentinan for malignant pleural effusions, lentinan was not administered intravenously, but with intrathoracic infusions [16].

Study results indicated that lentinan can be useful to improve response rate, 1-year survival, performance status, quality of life and radio/chemotherapy toxicity when administered in adjunct to standard care for some lung and gastrointestinal cancers. In particular, lentinan integrative therapy was able to ameliorate performance status and radio/chemotherapy toxicity in patients with esophageal, gastric and colorectal cancer, whereas it was capable of improving response rate and adverse effects of standard therapy in subjects with lung malignancies. Individuals with advanced-stage solid tumors also benefited from lentinan integrative supplementation in terms of 1-year survival rate and health-related quality of life.

When evaluated with the NIH tool, all included studies were judged as characterized by a fair-to-good methodological quality. However, in some meta-analyses, literature search strategies and the risk-of-bias assessment were poorly described. Evidence from included meta-analyses and results of the study quality assessment were summarized in Table 1.

Table 1. Summary of evidence from included meta-analyses about lentinan for integrative cancer treatment.

Population	Intervention	Comparison	Outcome	Results	Study Design	RQ	Ref.
Esophageal cancer	Lentinan + RT	RT	Response Rate, Performance Status, Decrease in RT toxicity	RR (Resp. Rate) = 2.41 RR (PS) = 4.22 * RR (DAE: leukopenia) = 0.098 *	NMA (1 study)	A	[9]
Gastric cancer	Lentinan + XELOX chemotherapy	XELOX chemotherapy	Response Rate, Performance Status, Decrease in CT toxicity	RR (Resp. Rate) = NR RR (PS) = 2.04 RR (DAE: leukopenia) = 8.16 * RR (DAE: nausea/vomiting) = 9.04 *	NMA (2 studies)	A	[10]
Unresectable/recurrent gastric cancer	Lentinan + CT MST = 139 days *	CT MST = 114 days	Survival Rate, Response Rate	HR (Resp. Rate) = 0.80 *	SMA (5 studies)	B	[11]
Colorectal cancer	Lentinan + FOLFOX chemotherapy	FOLFOX chemotherapy	Response Rate, Performance Status, Decrease in CT toxicity	RR (Resp. Rate) = 1.42 RR (PS) = 2.72 * RR (DAE: leukopenia) = 0.38 RR (DAE: nausea/vomiting) = 0.43	NMA (1 study)	A	[12]
Advanced (gastrointestinal, liver and lung) cancer	Lentinan + CT	CT	1-year Survival Rate, Response Rate, PoD, Decrease in CT toxicity	RR (1-y Surv. Rate) = 1.46 * RR (Resp. Rate) = 1.28 * RR (PoD) = 0.57 * RR (nonsevere AE) = 0.88 * RR (severe AE) = 0.73 *	SMA (17 studies)	A	[13]
Lung cancer	Lentinan + CT Resp. Rate = 56.9%*	CT Resp. Rate = 43.3%	Response Rate	RR (Resp. Rate) = 0.79 *	SMA (38 studies)	B	[14]
Non-small cell lung cancer	Lentinan + CT	CT	Response Rate, Decrease in CT toxicity	RR (Resp. Rate) = 1.31 * RR (DAE) = 0.54 *	SMA (12 studies)	B	[15]
Malignant pleural effusion [1]	Lentinan (intrapleural infusion) + CT	CT	Response Rate, QoL, Decrease in CT toxicity	RR (Resp. Rate) = 1.68 * RR (QoL) = 1.51 * Reduction in gastrointestinal and hematological CT toxicity	SMA (65 studies)	A	[16]

* Significant difference ($p < 0.05$) between intervention and control in favor of lentinan-adjuncted integrative therapy. [1] Causes of malignant pleural effusions included lung, breast and ovarian cancer. Legend: AE = adverse effects. CT = chemotherapy. DAE = decrease in chemo/radiotherapy adverse effects. MA = meta-analysis. MST = median survival time. NMA = network meta-analysis. NR = not reported. PoD = progression of disease. PS = performance status. QoL = health-related quality of life. RQ = review quality: A = good quality; B = fair quality; C = poor quality. RR = relative risk. RT = radiotherapy. SMA = standard meta-analysis.

4. Discussion

The mechanism of action of lentinan is not fully clear yet. Laboratory studies indicate that beta-glucans may serve as T-cell specific immune adjuvants and, in particular, lentinan seems capable of increasing the cytotoxicity of immune cells like macrophages and

some lymphocytes [17,18]. Moreover, lentinan may increase the production of various interleukins, including IL-4, IL-12, TNF-alpha and IFN-gamma [19,20]. In particular, it has been hypothesized that lentinan may modulate the immune function of oncologic patients in such a way as to restore their Th1-Th2 lymphocyte balance, which is usually impaired and characterized by a predominance of Th2 cells [1]. Additionally, a direct antineoplastic effect and a synergistic action with common chemotherapeutic drugs (docetaxel, cisplatin, gemcitabine) have been demonstrated in some laboratory experiments [1,3].

With regard to clinical tolerability, although data are scant, lentinan is considered as quite safe and the majority of possible adverse reactions following its supplementation are usually self-limiting, with more severe side effects (anaphylactoid reaction, chest pain, fever, granulocytopenia and elevated liver enzymes) mostly occurring for parenteral administration when infusion is excessively rapid [1,3,21,22]. However, allergic individuals and subjects who develop shiitake dermatitis [23] after mushroom consumption must avoid lentinan. Moreover, children, pregnant and breastfeeding women should not be given lentinan because of unknown health risks in these categories of patients. Furthermore, subjects with autoimmune disorders should not take lentinan due to the possibility of disease relapses and caution is required in patients with hepatic illnesses [24]. In general, safety data about lentinan are quite limited and, therefore, additional investigations are recommended. For this reason, its administration should be supervised and evaluated on a case-by-case basis.

In conclusion, available evidence suggests that lentinan may be considered as a valid integrative therapeutic option to administer in adjunct to radio/chemotherapy for selected patients with some solid tumors. Nevertheless, further studies are advised to better understand not only all potential drug interactions, side effects and long-term outcomes, but also disease- and patient-related predictors of efficacy of this complementary therapy.

Author Contributions: Conceptualization, M.A.; methodology, M.A., D.D. and F.F.; validation, M.A., D.D. and F.F.; investigation, M.A., D.D. and F.F.; resources, M.A., D.D. and F.F.; data curation, M.A., D.D. and F.F.; writing—original draft preparation, M.A., D.D. and F.F.; writing—review and editing, M.A., D.D. and F.F.; visualization, M.A., D.D. and F.F.; supervision, M.A., D.D. and F.F.; project administration, M.A.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data sharing not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Zhang, M.; Zhang, Y.; Zhang, L.; Tian, Q. Mushroom polysaccharide lentinan for treating different types of cancers: A review of 12 years clinical studies in China. *Prog. Mol. Biol. Transl. Sci.* **2019**, *163*, 297–328, doi:10.1016/bs.pmbts.2019.02.013.
2. Ina, K.; Kataoka, T.; Ando, T. The use of lentinan for treating gastric cancer. *Anticancer Agents Med. Chem.* **2013**, *13*, 681–688, doi:10.2174/18715206113130500002.
3. Memorial Sloan Kettering Cancer Center. Lentinan. Available online: https://www.mskcc.org/cancer-care/integrative-medicine/herbs/lentinan (accessed on 30 September 2020).
4. Shah, S.K.; Walker, P.A.; Moore-Olufemi, S.D.; Sundaresan, A.; Kulkarni, A.D.; Andrassy, R.J. An evidence-based review of a Lentinula edodes mushroom extract as complementary therapy in the surgical oncology patient. *JPEN J. Parenter. Enteral Nutr.* **2011**, *35*, 449–458, doi:10.1177/0148607110380684.
5. Chihara, G.; Hamuro, J.; Maeda, Y.Y.; Shiio, T.; Suga, T.; Takasuka, N.; Sasaki, T. Antitumor and metastasis-inhibitory activities of lentinan as an immunomodulator: An overview. *Cancer Detect. Prev. Suppl.* **1987**, *1*, 423–443.
6. Fusar-Poli, P.; Radua, J. Ten simple rules for conducting umbrella reviews. *Evid. Based Ment. Health* **2018**, *21*, 95–100, doi:10.1136/ebmental-2018-300014.
7. Bramer, W.M.; Rethlefsen, M.L.; Kleijnen, J.; Franco, O.H. Optimal database combinations for literature searches in systematic reviews: A prospective exploratory study. *Syst. Rev.* **2017**, *6*, 245, doi:10.1186/s13643-017-0644-y.

8. Study Quality Assessment Tools. Available online: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools (accessed on 30 September 2020).
9. Zhang, D.; Ni, M.; Wu, J.; Liu, S.; Meng, Z.; Tian, J.; Zhang, X.; Zhang, B. The Optimal Chinese Herbal Injections for Use with Radiotherapy to Treat Esophageal Cancer: A Systematic Review and Bayesian Network Meta-Analysis. *Front. Pharmacol.* **2018**, *9*, 1470, doi:10.3389/fphar.2018.01470.
10. Zhang, D.; Wu, J.; Wang, K.; Duan, X.; Liu, S.; Zhang, B. Which are the best Chinese herbal injections combined with XELOX regimen for gastric cancer?: A PRISMA-compliant network meta-analysis. *Medicine* **2018**, *97*, e0127, doi:10.1097/MD.0000000000010127.
11. Oba, K.; Kobayashi, M.; Matsui, T.; Kodera, Y.; Sakamoto, J. Individual patient based meta-analysis of lentinan for unresectable/recurrent gastric cancer. *Anticancer Res.* **2009**, *29*, 2739–2745.
12. Zhang, D.; Wu, J.; Duan, X.; Wang, K.; Ni, M.; Liu, S.; Zhang, X.; Zhang, B.; Zhao, Y. Network Meta-Analysis of Chinese Herbal Injections Plus the FOLFOX Regimen for the Treatment of Colorectal Cancer in China. *Integr. Cancer Ther.* **2019**, *18*, 1534735419827098, doi:10.1177/1534735419827098.
13. Wang, H.; Cai, Y.; Zheng, Y.; Bai, Q.; Xie, D.; Yu, J. Efficacy of biological response modifier lentinan with chemotherapy for advanced cancer: A meta-analysis. *Cancer Med.* **2017**, *6*, 2222–2233, doi:10.1002/cam4.1156.
14. Zhang, Y.; Zhang, M.; Jiang, Y.; Li, X.; He, Y.; Zeng, P.; Guo, Z.; Chang, Y.; Luo, H.; Liu, Y.; et al. Lentinan as an immunotherapeutic for treating lung cancer: A review of 12 years clinical studies in China. *J. Cancer Res. Clin. Oncol.* **2018**, *144*, 2177–2186, doi:10.1007/s00432-018-2718-1.
15. Yin, X.; Ying, J.; Li, L.; Zhang, H.; Wang, H. A meta-analysis of lentinan injection combined with chemotherapy in the treatment of nonsmall cell lung cancer. *Indian J. Cancer* **2015**, *52*, 29–31, doi:10.4103/0019-509X.168953.
16. Xiao, Z.; Jiang, Y.; Chen, X.-F.; Wang, C.-Q.; Zheng, X.-T.; Xu, W.-H.; Zou, X.-X.; Zhou, J.-M.; Yang, Y.-H.; Hu, S.-S.; et al. Intrathoracic infusion therapy with Lentinan and chemical irritants for malignant pleural effusion: A systematic review and meta-analysis of 65 randomized controlled trials. *Phytomedicine* **2020**, *76*, 153260, doi:10.1016/j.phymed.2020.153260.
17. Hamuro, J.; Röllinghoff, M.; Wagner, H. Induction of cytotoxic peritoneal exudate cells by T-cell immune adjuvants of the beta(1 leads to 3) glucan-type lentinan and its analogues. *Immunology* **1980**, *39*, 551–559.
18. Hamuro, J.; Röllinghoff, M.; Wagner, H. beta(1 leads to 3) Glucan-mediated augmentation of alloreactive murine cytotoxic T-lymphocytes in vivo. *Cancer Res.* **1978**, *38*, 3080–3085.
19. Dong, S.-F.; Chen, J.-M.; Zhang, W.; Sun, S.-H.; Wang, J.; Gu, J.-X.; Boraschi, D.; Qu, D. Specific immune response to HBsAg is enhanced by beta-glucan oligosaccharide containing an alpha-(1→3)-linked bond and biased towards M2/Th2. *Int. Immunopharmacol.* **2007**, *7*, 725–733, doi:10.1016/j.intimp.2007.01.004.
20. Kupfahl, C.; Geginat, G.; Hof, H. Lentinan has a stimulatory effect on innate and adaptive immunity against murine Listeria monocytogenes infection. *Int. Immunopharmacol.* **2006**, *6*, 686–696, doi:10.1016/j.intimp.2005.10.008.
21. Gordon, M.; Bihari, B.; Goosby, E.; Gorter, R.; Greco, M.; Guralnik, M.; Mimura, T.; Rudinicki, V.; Wong, R.; Kaneko, Y. A placebo-controlled trial of the immune modulator, lentinan, in HIV-positive patients: A phase I/II trial. *J. Med.* **1998**, *29*, 305–330.
22. Wada, T.; Nishide, T.; Hatayama, K.; Chang, S.W.; Tatsuta, M.; Yasutomi, M. A comparative clinical trial with tegafur plus lentinan treatment at two different doses in advanced cancer. *Gan To Kagaku Ryoho Cancer Chemother.* **1987**, *14*, 2509–2512.
23. Nguyen, A.H.; Gonzaga, M.I.; Lim, V.M.; Adler, M.J.; Mitkov, M.V.; Cappel, M.A. Clinical features of shiitake dermatitis: A systematic review. *Int. J. Dermatol.* **2017**, *56*, 610–616, doi:10.1111/ijd.13433.
24. Firenzuoli, F. *Interazioni fra Erbe, Alimenti e Farmaci*; Tecniche Nuove: Milano, Italy, 2009; ISBN 9788848120685.