

News Release

Title

Phlebotomy as a preventive measure for crocidolite-induced mesothelioma in male rats

Key Points

- Phlebotomy prolonged long-term survival in crocidolite (blue asbestos)-induced mesothelioma in male rats.
- Phlebotomy significantly decreased the tumor weight and nuclear grade of malignant mesothelioma, and modestly reduced the associated ascites.

Summary

Malignant mesothelioma (MM) is a rare but socially important neoplasm due to its association with asbestos exposure. While MM is difficult to diagnose at an early stage, there are no particularly effective treatments available at the advanced stage, thus necessitating efficient strategies to prevent MM in individuals already exposed to asbestos. We previously showed that persistent oxidative damage caused by foreign body reaction and affinity of asbestos both to hemoglobin and histones is one of the major pathogeneses. Accordingly, as an effective strategy to prevent asbestos-induced MM, we undertook the use of an iron chelator, deferasirox, which decreased the epithelial-mesenchymal transition in a crocidolite-induced rat MM model. However, this agent may exhibit adverse effects. Here, we studied the effects of iron removal by phlebotomy as a realistic measure on the same rat model. We injected a total of 5 mg of crocidolite intraperitoneally to F1 hybrid rats between the Fischer-344 and Brown-Norway strains at the age of 6 weeks. We repeated weekly or biweekly phlebotomy of 6 to 8 ml/kg/time from 10 to 60 weeks of age. The animals were observed until 120 weeks. In male rats, phlebotomy significantly decreased the weight and nuclear grade of MM, and modestly reduced the associated ascites and the fraction of more malignant sarcomatoid subtype. Weekly phlebotomy prolonged the long-term survival. Our results indicate that appropriate phlebotomy may be a practical preventive measure to attenuate the initiation and promotion capacity of asbestos towards MM by reducing iron in individuals exposed to asbestos.

Research Background

Malignant mesothelioma (MM) is a neoplasm caused primarily by asbestos exposure. Asbestos is one of the natural fibrous silicate minerals, consisting of several types such as crocidolite (blue asbestos), amosite (brown asbestos) and chrysotile (white asbestos). The former two contain iron as ~30% of their components. Asbestos is now recognized as a

human carcinogen, and its use is legally prohibited in most of the developed countries but not yet banned in the developing countries. In Japan, the number of MM patients will peak in 2025, and 100,000 new patients are expected in the coming 40 years. MM is one of the most aggressive tumors when diagnosed, and the median survival is expected to be 4-18 months for pleural forms. Therefore, it is important to develop preventive intervention in high-risk people exposed to asbestos.

Research Results

We injected a total of 5 mg of crocidolite intraperitoneally to F1 hybrid rats between the Fischer-344 and Brown-Norway strains at the age of 6 weeks. We divided the rats that received crocidolite into the following two groups: non-therapeutic (NT) and phlebotomy four times per month (Phleb-4), which is a calculated research design for rats based on the present human clinical applications. We repeated weekly phlebotomy from 10 to 60 weeks of age. The animals were observed until 120 weeks.

We modified the dose of phlebotomy, if necessary, and the hematocrit was maintained constant but significantly lower than that of the NT group.

Phlebotomy of the Phleb-4 group revealed a tendency to prolong the disease-specific survival rate after crocidolite injection in males ($P = 0.0539$; **Fig. a**).

At autopsy, MM were observed as distinct large nodules at various locations in the peritoneal cavity, including the hepatic surface, greater omentum, mesentery and epididymal adipose tissue (**Fig. b**). We collected and weighed the tumors and ascites induced. The tumor weight was significantly lower in male Phleb-4 rats ($P = 0.039$; **Fig. c**) than in male NT rats. The amounts of ascites tended to be lower in male Phleb-4 rats than in male NT rats. Phlebotomy significantly decreased the histological atypia of MM ($P = 0.0456$). These results suggest that iron reduction by phlebotomy may be useful for MM prevention in humans already exposed to asbestos. In this rat model, we obtained positive results only in males, which we believe results from difference in iron metabolism in female rats.

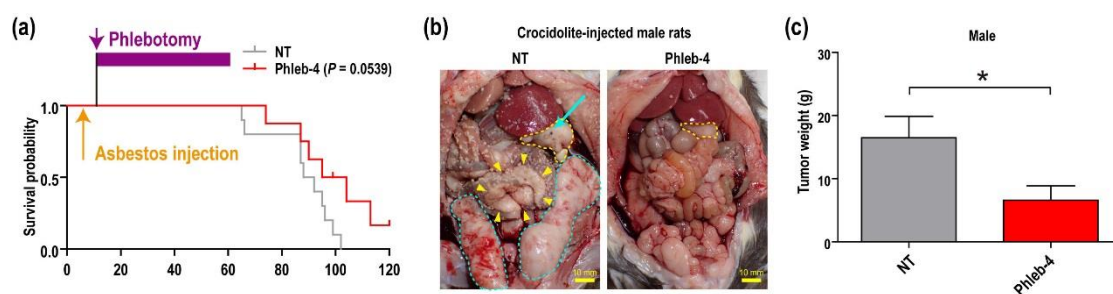


Figure. The preventive effects of phlebotomy on mesothelioma

(a) Disease-specific survival rate of male rats. Male rats that underwent phlebotomy four

times per month (Phleb-4) tended to survive longer than male rats injected with 5 mg crocidolite that did not receive therapy (NT; $P = 0.0539$). (b) Macroscopic findings at autopsy. Greater omentum (yellow dotted line), mesentery (yellow arrowheads), and epididymal adipose tissues (blue dotted line) were replaced by the primary tumor of non-therapeutic (NT) rats (left). Countless disseminated minute tumors of MM were observed in the whole peritoneal cavity (left). Blue arrow indicates residual crocidolite on MM of the greater omentum. Only primary tumor was observed on the hepatic surface and greater omentum (right, yellow dotted line) and dissemination was not observed in rats that underwent phlebotomy four times per month (Phleb-4; right). Scale bar = 10 mm. (c) Tumor weight of male rats. Tumor weight was significantly lower in male Phleb-4 rats than in male NT rats ($P = 0.039$).

Research Summary and Future Perspective

The present preclinical study suggests that appropriate phlebotomy is effective as a preventive measure for asbestos-induced MM carcinogenesis, regarding tumor size, ascites, histology and disease-specific survival. At least, it delays tumor progression. Phlebotomy is a relatively safe intervention in humans and has been shown to decrease the visceral cancer incidence and mortality in humans. If the high-risk individuals are not iron-deficient, we recommend considering regular phlebotomy. Clinical trials are necessary for confirmation of the present results.

Publication

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