Randomised Trial of Vitamin A Versus Observation as Adjuvant Therapy in High Risk Primary Malignant Melanoma.

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Summary of Trial

Meyskens et al reported on a national cooperative group trial looking at the role of adjuvant oral vitamin A in the treatment of high risk primary melanoma patients following definitive local surgery. This is a randomised controlled trial conducted between August 1981 and March 1987. In that time period the trial accrued three hundred and eighty six patients. The aim of the study was to assess it oral vitamin A was superior to observation alone in terms of both the disease free survival and overall survival. The study found no advantage with vitamin A in terms of disease free survival or overall survival.

Design Features

It is known that vitamin A causes differentiation of epithelial tissue. Vitamin A has been trialled by many investigators, such as Hoy et al who used 13 cis-retinoic acid for patients with dysplasia in the head and neck and found differentiation of the lesions occurred.

Specifically for skin cancers, pilot studies were undertaken in the 1970's. A pilot study allows investigators to establish if treatment is able to be tolerated. A report by Levine in 1980 indicated that topically applied retinoic acid could cause regression of metastatic melanoma nodules.

The total vertical height of melanoma is the single most important prognostic factor for stage I and stage II disease. High risk patients for the purposes of the trial were defined as those with stage IB, stage IIA and stage IIB.

The aim included the end points to be examined by the study, those of disease free survival and overall survival. Disease free survival was defined as the time from registration to the time of disease progression or death, whichever occurred first. Overall survival was defined as the time from registration to death. It is important also to examine the toxicity of the treatment since a large number of patients will be cured by surgery alone. The treatment must therefore be well tolerated and free of long term side effects.

The study is designed as a randomised clinical trial. The advantages of a randomised trial are firstly, it allows of the eligibility criteria, intervention and outcome assessment. Secondly, it allows for the use of statistical methods which will have few inbuilt assumptions. Thirdly, it provides the best chance of obtaining strong evidence of a cause and effect. A randomised trial is therefore better than a prospective single arm study using historical controls.

In a controlled trial such as this one, the experimental and control groups should be treated alike in all ways except for the drug (vitamin A). Therefore any difference between the groups will be due to the vitamin A and not to other factors. To reduce the chances that subjects or investigators see what they want to sturdy then a double blind trial can be undertaken. Therefore neither the subject nor the investigators know whether the subject is in the treatment or the observation arm. If the subject only is unaware of the arm they have been allocated this is a blind trial. It would have been easy in this paper to have had a double blind trial. The vitamin A was given in oral form and a placebo could have been supplied for the observation arm. Midway through the trial the active ingredient was changed from retinol to retinol palmitate. The assumption being that both agents were equally as active.

The source of the subjects were from a number of American Centers cooperating for this trial, although the number of participating centers is not clearly stated. It appears from the first page of the paper in the acknowledgments that there may have been nine participating centres.

The eligibility criteria were clearly stated. Histologically the melanoma was greater than 0.75 mm thickness in vertical height. The melanoma resected had to have an adequate local excision (initially 3 cm. margin but due to change in standard practice this became 1 cm.). Regional lymph node resection was not required, however if performed the lymph nodes had to be histologically free of involvement by melanoma. There was no age restriction but the patient had to be enrolled into the trial within 16 weeks of surgical resection of the primary.

The exclusion criteria were not clearly stated. The paper mentions the investigations in a pretreatment evaluation to exclude patients with detectable residual or metastatic disease. There was no comment on patient factors that may preclude patients from entering the trial. For example a patient with a previous diagnosis of malignancy or a preexisting medical condition that would prevent vitamin A at these dosages being used, therefore one assumes these patients were

not excluded.

There was no power based assessment of the adequacy of the sample size. A paper should determine the power of the study. It consists of determining how large a sample size is required to detect an actual difference of some specified magnitude. The power of the study should be determined prior to beginning the study. If it is not determine then the study may require more time and resources than are available. Alternatively the study may use more subjects than needed and therefore waste resources. Without information about the power of the study then it is difficult to derive a conclusion from a negative study.

Conduct of Study

There were three hundred and eighty six patients accrued over a five and a half year period. There was no indication as to the contribution from each involved centre. In multicentre trials this is important since it there is a marked difference from one of the involved centres then the reason for this would need to be explained.

The patients were stratified prior to randomisation by :- depth of invasion (Breslow's thickness), sex and type of therapy (excision, excision + nodal dissection, excision + perfusion and excision + both nodal dissection and perfusion). Characteristics used to stratify should always be related to the measurement of interest. In these cases stratified random sampling is the most efficient - requiring the smallest sample size. The patients were randomised after surgical excision of the high risk melanoma. The paper failed to inform the reader about the method of randomisation. The authors that report the randomisation method provide some assurance to the reader that randomisation did occur. It is also important that the contributing physician is not able to predict which arm their patient will be allocated. If the physician can predict which arm then it may influence his or her choice to enter a patient and this would introduce bias into the study.

The eligible patients gave consent for the trial prior to randomisation. They were informed of the design and aim of the study as well as the possible toxicity if they were allocated to the treatment arm. By obtaining informed consent prior to randomisation the patient is accepting whichever treatment they are allocated. It also indicates to the patient that their treating physician does not know which treatment arm is better.

In multicentre trials it is important to have a quality assurance program. The central office for the trial must be able to verify that the patients in the trial fulfill the eligibility criteria. In this paper all histopathology was reviewed by one central pathologist. Upon review a large number of patients were deemed ineligible.

Statistical Analysis

There were three hundred and eighty six patients registered with high risk primary melanoma during the trial period. There were one hundred and forty six patients that were excluded since they were found to be ineligible due to entry criteria violations. The reasons for ineligibility were as follows : surgical margins less than 3 cm. (68 patients); surgical treatment which was inadequate and one assumes for histopathological reasons (3 patients); inadequate material submitted for either surgical or pathological review (46 patients); inadequate tumour thickness (19 patients); and other violations of protocol eligibility - including misdiagnosis and insufficient prerandomisation investigations (10 patients). These patients had been randomised but were not found ineligible until the time of review. All of the previous exclusions occurred after review with the majority occurring after pathological review. The slides of all of the patients were reviewed by one central pathologist. These conditions were present at the time of randomisation but not detected. Since these patients did not satisfy the histopathological requirements then it was valid to declare them ineligible.

The paper shows the pretreatment stratification characteristics for the two arms in tabular form and the characteristics were equivalent. There are no major differences between the two arms of the study. If a major difference were to be present then this can impact on the overall results.

Statistical analysis for disease free survival and overall survival were conducted in the Cox proportional hazards regression framework. In studies of overall survival or disease free survival, the investigators cannot wait until all patients in the study die or recur. Censored observations is where the patients have been observed for unequal lengths of time and therefore the outcome is not known for all of the group. A regression technique was developed by Cox in 1972 for when there are time dependent censored observations. It allows independent variables in the regression equation to vary with time. A hazard function implies the probability that the patient dies during a specified time interval, given that the patient lived until the beginning of that interval.

The Cox proportional hazard model is an appropriate way to examine the disease free survival and overall survival. There was no difference between the observation arm and those receiving adjuvant vitamin A. Further analysis was performed to determine if there was a difference in either disease free survival or overall survival for the stratification factors. The data was not shown for either sex or lymph node management. The reader was asked to accept the fact that there was no difference caused by these two factors. The data should have been presented for the reader to make up his own mind.

The trial showed both disease free survival and overall survival for thickness of the primary lesion. The investigators found a possible trend for improvement in overall survival but not disease free survival for primary lesions between 1.51 and 3.00 mm. This trial was not designed with sufficient power for subset analysis. Therefore it is difficult to draw

any conclusion from a trend in improvement in overall survival for a lesion between 1.51 and 3.00 mm.

The treatment arm was associated with significant toxicity. 14% of the patients ceased treatment due to vitamin A toxicity. The toxicities were rated according to the SWOG guidelines with the severity of the side effect being recorded. By using a standard system for toxicity it allows for comparison with other vitamin A trials. Vitamin A as a number of unique side effects. They include effects on the CNS, dermatological, and endocrine systems. These grades of toxicity were based on the known side effects at the time of commencing this trial. Since that time there has been much more information gathered as to the side effects of retinoids. Therefore future vitamin A trials would have better developed toxicity guidelines. As well as the best treatment schedule and dose of vitamin A.

Conclusion

This is a negative study which found no improvement in either disease free survival or overall survival with the use of adjuvant vitamin A. There was no power based assessment. The ramifications of not performing power calculations can be very serious. In other words, a study may have low power because the sample size was too small to detect the presence of reasonable differences. The conclusion drawn by the authors is that since there is no overall survival benefit, then no further evaluation of vitamin A is warranted as adjuvant therapy for melanoma. The conclusion from this trial is not justified.